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CUTANEOUS CARCINOMA

I. A STATISTICAL ANALYSIS WITH RESPECT TO THE DURATION AND SIZE OF THE TUMORS AND THE AGE OF THE PATIENTS AT ONSET AND AT BIOPSY OF TUMOR

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Just as zoology consists in the classification of animals into species and the study of the natural history of these species, oncology involves the classification of cancer into types and the study of the "natural history" of these types.

Although cutaneous tumors of the carcinoma group are very suitable for the study of the natural history of a tumor type, few analyses of data on these tumors have been published. Various aspects of basal cell and epidermoid or squamous cell carcinoma of the skin were studied by Broders,[1] Geschickter and Koehler,[2] Pack and LeFevre [3] Lacassagne,[4] Magnusson [5] and Warren, Gates and Butterfield.[6]

The present series of articles gives a detailed analysis of data on such tumors as taken from the records of the Collis P. Huntington Memorial Hospital and the Pondville Hospital. This investigation includes particularly (1) the similarities and differences between basal cell and epidermoid carcinoma, (2) the characteristics of value in differential diagnosis, (3) the efficacy of treatment and (4) the value of grading.

From the laboratories of pathology of the Pondville Hospital, Wrentham, Mass., and the Collis P. Huntington Memorial Hospital, Boston.

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1. Broders, A. C.: J. A. M. A. **72**:856, 1919; Ann. Surg. **73**:141, 1921.
2. Geschickter, C. F., and Koehler, H. P.: Am. J. Cancer **23**:804, 1935.
3. Pack, G. T., and LeFevre, R. G.: J. Cancer Research **14**:167, 1930.
4. Lacassagne, A.: Ann. de dermat. et syph. **4**:497, 613 and 722, 1933.
5. Magnusson, A. H. W.: Acta radiol., 1935, supp. 22, p. 1.
6. Warren, S.; Gates, O., and Butterfield, P. W.: New England J. Med. **215**:1060, 1936.

METHODS

In studying the natural history of a specific type of tumor, it is necessary to analyze a large group of cases. Such an analysis requires the use of statistical methods.

Unfortunately, there are no standardized statistical methods for the study of tumors. It is therefore frequently difficult or impossible to compare the results obtained by different institutions or to compare the efficacy of various methods of treatment.

In the present study some new statistical devices have been used and found to be of value. It is believed that these methods could be applied to investigations of the natural history of other types of tumor. To summarize, this series of articles considers the natural history of two types of cutaneous carcinoma and presents new statistical methods for analyzing a group of tumors.

CASES USED

Three series of cases are used in this analysis. One series consists of 495 cases recorded at the Pondville Hospital in which biopsies were made and in which the biopsy specimens were adequate for a determination of the type of tumor. These cases cover the years from 1927, when the hospital was opened, to the end of 1936.

The Huntington Hospital series (581 cases) includes nearly all cases in which biopsies were made from January 1929 to May 1937 and some of the cases which were collected by Warren, Gates and Butterfield for another study.[6]

A third series comprises 2,124 cases recorded at the Massachusetts Tumor Diagnostic Service during the years 1912 to 1935 and includes all biopsy specimens from Huntington Hospital and surgical specimens sent in by various hospitals and physicians of Massachusetts.

In all cases the final pathologic diagnosis was made by Dr. Shields Warren.

Cases of carcinoma of the genitalia and of carcinoma arising at the mucocutaneous junction of the lips and of the anus are not used in this study.

DURATION

The duration of each cutaneous tumor was obtained from the clinical history as given by the patient to the resident and visiting surgeons of the Pondville or the Huntington Hospital. Many of the lesions were treated before hospitalization, with partial or complete regression and subsequent recurrence, but in all cases the duration was calculated from the onset of the original tumor and not from the time of the last recurrence. When the tumor arose from a birthmark, the change in character of the lesion was taken as the time of onset. This change was, of course, much more difficult to detect accurately than that marking the origin of a tumor in a normal area of skin. The accuracy of the

determination of duration depended on the skill of the clinician as an examiner and on the patient's powers of observation and memory.

In view of the difficulties, the errors of the estimations of duration were undoubtedly large. However, certain definite conclusions could be established, as will be shown in this and subsequent papers.

The tumors diagnosed as basal cell and epidermoid carcinoma in the two hospitals are compared as to the duration in chart 1 by means of frequency polyons. The four frequency distributions of chart 1 are represented more satisfactorily in chart 2 as cumulative frequency curves constructed on logarithmic probability paper.[7]

The same data are represented in charts 1 and 2. In chart 1, where duration is constructed on an arithmetic scale, the polygons are obviously asymmetric. In chart 2, however, where duration is represented on a logarithmic scale, the curves are rectilinear and symmetric. It seems, then, that the distributions are symmetric in a logarithmic but not in an arithmetic graph.

It is seen from both charts that the frequency distributions for the two types of cutaneous carcinoma differ markedly. Chart 2 shows that the average patient postponed hospitalization three and a half (3.5) years if he had a basal cell tumor but waited only one and a fifth (1.2) years if he had an epidermoid tumor. Apparently some factor other than duration influenced the patient with a tumor to seek medical aid in a hospital.

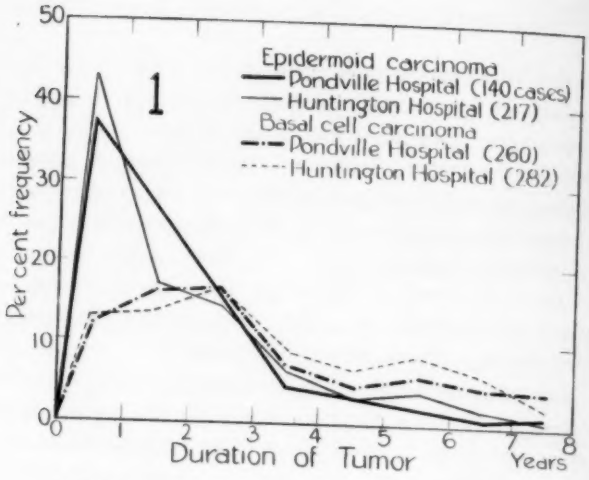
The difference in the duration of epidermoid and basal cell carcinoma is emphasized in chart 3. The chart shows that of the patients who stated that they had the cutaneous lesions less than six months, 22 per cent had basal cell and 78 per cent epidermoid carcinoma. Of the patients who claimed that their lesions were present at least five and a half years, more than 80 per cent had basal cell carcinoma. The duration of the tumor is, it seems, an aid in the clinical diagnosis of the type of carcinoma.

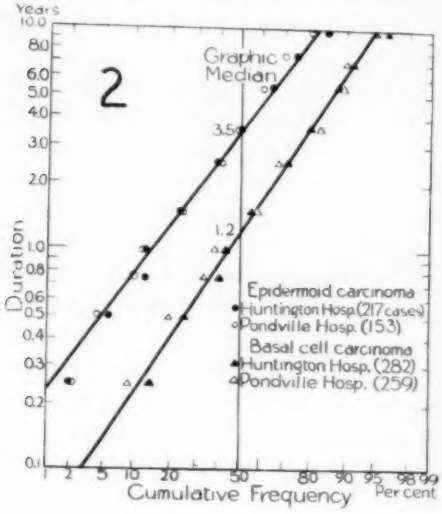
According to charts 1 and 2, the frequency curves for the same type of tumor in the Pondville and the Huntington Hospital series are approximately the same. In fact, the corresponding distributions in chart 2 are practically identical and can be represented by a single line. It seems then that the surgeons of the two hospitals obtained similar estimations of duration.

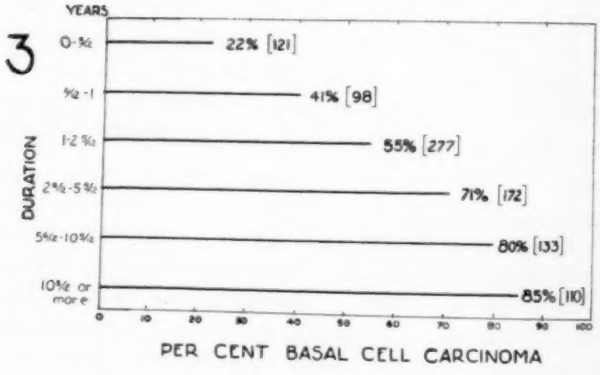
SIZE

The maximum diameter of each tumor at the time of the hospitalization of the patient was used as a measure of the size. The dimensions of the lesions were determined by the clinician usually by inspection without resort to a ruler. In a few cases the clinician used animal or vegetable units—for example, man's palm, queen olive. Many of the

7. Schrek, R., and Lipson, H. I.: Human Biol. **13**:1, 1941.







Charts 1-2-3

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lesions were excised and measured by the pathologist without allowing for skin shrinkage. In general, there was good agreement between the clinician's and the pathologist's estimations. The size finally used for each lesion was a compromise weighted in favor of the pathologist's report.

The maximum diameters of basal cell and of epidermoid tumors in the Huntington Hospital series are compared in chart 4 by means of logarithmic probability paper.

The two distributions are approximately the same and can be represented by a single straight line, with a median of 19 mm. The rectilinearity of the curve indicates that the frequency distributions for size are symmetric. It may be concluded that patients with basal cell and with epidermoid carcinoma have lesions of approximately the same size at the time of hospitalization.

Of lesions observed at Pondville Hospital, the graphic median is 24 mm. for epidermoid carcinoma (161 cases) and 22 mm. for basal cell carcinoma (251 cases). The tumors at Pondville Hospital are slightly larger (3 to 5 mm.) than those at Huntington Hospital.

AGE AT TIME OF BIOPSY

The age distributions of patients with epidermoid and with basal cell carcinoma of the skin are compared in chart 5 by cumulative frequency curves constructed on arithmetic probability paper. The graphs were constructed from data of the Massachusetts Tumor Diagnostic Service.

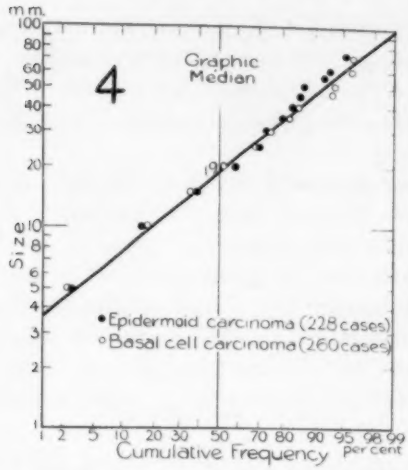
The chart shows that the median age of patients with basal cell carcinoma was 63.0 years, as compared with 67.2 years for patients with epidermoid carcinoma. The difference, 4.2 years, was small but, according to chart 5, statistically significant.

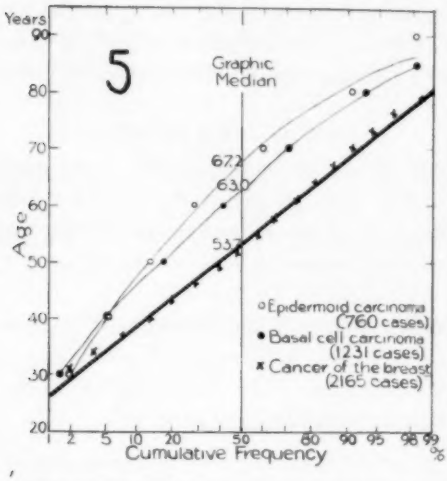
EXPLANATION OF CHARTS 1, 2 AND 3

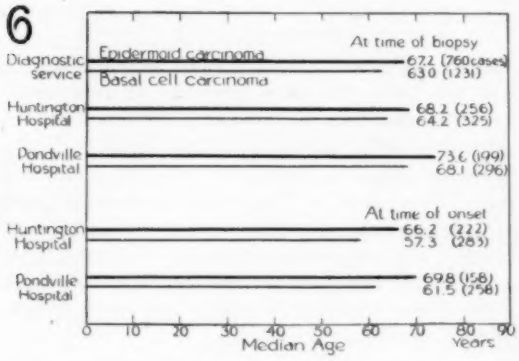
Chart 1.—Frequency polygons of the durations of two types of cutaneous carcinoma: epidermoid and basal cell. The polygons are asymmetric. Corresponding polygons of the two hospitals are similar. The durations of the basal cell tumors were in general greater than those for the epidermoid tumors.

Chart 2.—Cumulative frequency curves of the durations of epidermoid and basal cell carcinoma, constructed on logarithmic probability paper. This chart represents the same data as chart 1. The curves are linear (indicating normal frequency distributions) and approximately parallel (indicating equal variabilities). Corresponding curves of the two hospitals are identical. The median duration of basal cell carcinoma (three and a half years) was much greater than that of epidermoid carcinoma (one and a fifth years).

Chart 3.—The percentage of basal cell carcinoma according to duration. Cutaneous carcinoma having a duration of less than six months was basal cell in type in only 22 per cent of the cases; cutaneous carcinoma having a duration of five and one-half years or more was basal cell in 80 per cent of the cases.







Charts 4-5-6

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Chart 6 compares the median ages, graphically determined, of patients of the three series used in this study. The figures show, first, that the patients of Pondville Hospital were about four years older than the corresponding patients of Huntington Hospital and, second, that the median age of those with basal cell carcinoma in each series was four to five years less than the corresponding age of those with epidermoid carcinoma.

The age distributions, particularly that for patients with epidermoid carcinoma, are seen in chart 5 to be asymmetric. From chart 5, this asymmetry can be seen to be due either to a theoretically excessive number of young persons with cutaneous tumors or to an insufficient number of old persons.

The most plausible explanation for the asymmetry seems to be that the high mortality rate of persons past the median age of 67.2 years would decrease markedly the number of old people in whom epidermoid carcinoma could develop. The hypothesis was tested by constructing (chart 5) the cumulative frequency curve of the ages of patients with mammary carcinoma. The data for this curve, given in a paper by Nathanson and Welch,[8] were found to fit very satisfactorily a straight line (chart 5). This frequency distribution is then normal and symmetric. The symmetry is presumably associated with the relatively low median age of 53.7 years. It seems, then, that the asymmetry of the age incidence of cutaneous carcinoma is the result of the large mortality rate of persons past the high median age.

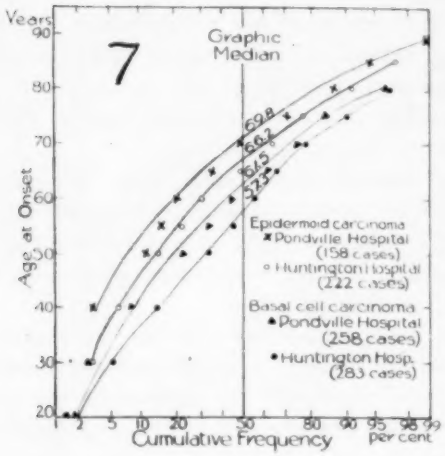
8. Nathanson, I. T., and Welch, C. E.: Am. J. Cancer **28**:40, 1936.

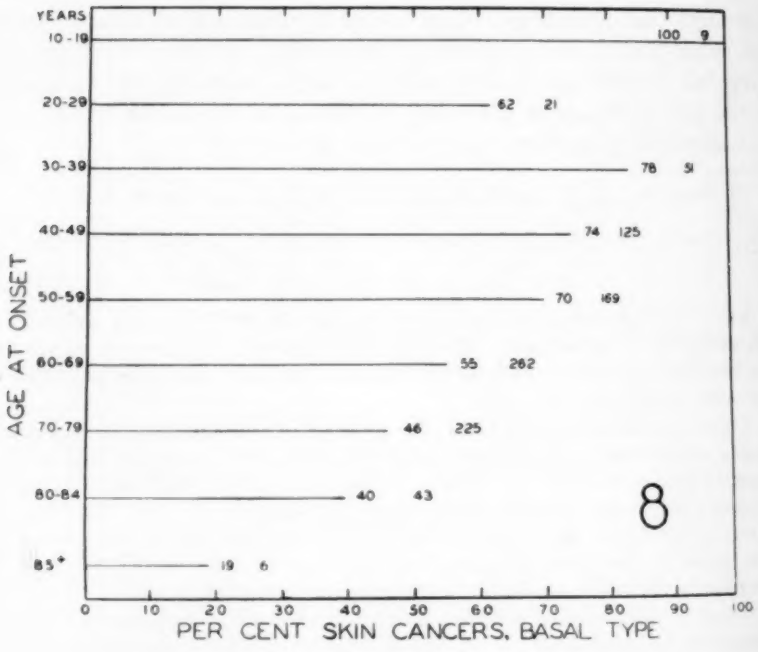
EXPLANATION OF CHARTS 4, 5 AND 6

Chart 4.—Cumulative frequency curve of the size of epidermoid and of basal cell carcinoma of Huntington Hospital. The frequency distributions of size for the two types of cutaneous carcinoma were similar and could be represented by the same straight line.

Chart 5.—Cumulative frequency curves of the age incidence of three types of tumors, constructed on arithmetic probability paper. The curve for the age incidence of epidermoid carcinoma has a median age of 67.2 years and is markedly nonlinear, indicating an asymmetric frequency distribution. The curve for the basal cell carcinoma has a median age of 63.0 years and has a slight curvature. The curve for the mammary carcinoma has a median age of 53.7 years and is linear and symmetric.

Chart 6.—Median ages of three series of patients with cutaneous carcinoma as determined for time of biopsy and for time of onset. The chart shows that the patients of Pondville Hospital were four to five years older than those of Huntington Hospital and of the Massachusetts Diagnostic Service. At time of biopsy the patients with basal cell carcinoma were about four years younger than the corresponding patients with epidermoid carcinoma; and at time of onset they were eight to nine years younger.





Charts 7-8

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AGE AT TIME OF ONSET

More important than the age at time of biopsy is the age of the patients at the time their tumors are first observed. This is especially true in regard to neoplasms of long duration, as these cutaneous lesions are. The age of each patient at onset was determined by subtracting the duration of the tumor (as reported by the patient) from the age of the patient at the time of hospitalization. The cumulative frequency curves for patients of Pondville and Huntington Hospitals are shown in chart 7 and summarized in chart 6.

All the curves in chart 7 are nonlinear or asymmetric. At Pondville Hospital the median age at time of onset for patients with epidermoid carcinoma was 69.8 years and that for patients with basal cell carcinoma was only 61.5. The corresponding figures for patients at Huntington Hospital were 66.2 and 57.3 years. Patients in whom

A Comparison of the Percentile Occurrence of Basal Cell Carcinoma in Different Age Groups of Patients of Huntington and Pondville Hospitals

	Percentage of Cases of Basal Cell Carcinoma in Given Age Group								
Series	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-84	85 or More
Huntington Hospital.....	100 (4)*	61 (18)	79 (33)	74 (33)	64 (99)	46 (138)	46 (111)	38 (24)	20 (5)
Pondville Hospital.....	100 (5)	67 (3)	78 (18)	75 (39)	79 (70)	65 (124)	46 (114)	42 (19)	18 (11)

* The figure in parenthesis is the total number of cases of cutaneous carcinoma in the age group on which the percentage is based.

basal cell carcinoma developed were, then, 8.3 and 8.9 years younger than those in whom epidermoid carcinoma developed. It should also be noted that the patients of Huntington Hospital were about four years younger than those of Pondville Hospital.

The differences in age of onset of the two types of cutaneous carcinoma are further analyzed in chart 8 and in the table. The chart shows that cutaneous carcinoma arising before 40 years of age is basal

EXPLANATION OF CHARTS 7 AND 8

Chart 7.—Cumulative frequency curves of the age incidence of the two types of cutaneous carcinoma at time of onset. The curves are (1) nonlinear, indicating asymmetric distribution, (2) distinctly separate from each other, indicating statistically significant differences in the median ages, and (3) approximately parallel, indicating approximately equal variability of the four frequency distributions.

Chart 8.—The percentage of cases of basal cell carcinoma according to age of onset. The figure at the left indicates percentage, and the figure at the right, the number of cases.

cell in type in about 80 per cent of the cases. That arising after 85 years of age is basal cell in only 19 per cent and epidermoid in 81 per cent of the cases.

The tumors in the age group 20 to 29 years have a lower percentage of the basal cell type than the tumors in the 30 to 39 year age group. This discrepancy has no statistical significance.

As can be seen in the table, the two hospitals gave consistent results in spite of the fact that the patients of Pondville Hospital are in general four to five years older than patients of Huntington Hospital.

COMMENT

Measurement of the Stage of Development of Cutaneous Tumors.— It is a well recognized fact that the results of treatment depend on the stage of development of the group of tumors. In this paper the development of cutaneous tumors is represented by the median size and the median duration. The former is the more accurate measure, as the size of the individual tumor can be determined more accurately than its duration.

With basal cell carcinoma, the average patient of Huntington Hospital waited three and a half years before hospitalization, but with epidermoid carcinoma he waited only one and a fifth years. On the contrary, the size of the cutaneous lesion in the average patient was the same (1.9 cm.) for both types of carcinoma. It seems, then, that it is the size of the tumor, not the duration, that prompts the patient to seek hospitalization.

It was observed in this work that the median size of Huntington Hospital tumors (1.9 cm.) was somewhat less than that of Pondville Hospital tumors (2.2 and 2.4 cm.). Therefore, the therapeutic results obtained in the former hospital might be expected to be somewhat better than those obtained in the latter.

The difference in the median sizes for the two clinics also indicates that the average patient of the Huntington Hospital is somewhat more alert to the danger of a cutaneous tumor than the average patient of Pondville Hospital. The two hospitals are known to serve slightly different classes of patients.

It appears from the foregoing that the awareness of patients toward cancer can be measured by the median size of the cutaneous lesions.

The state of Massachusetts has an extensive program for educating the laity and the physicians in regard to cancer. It should be of interest to redetermine the median size and duration of cutaneous tumors of Pondville and Huntington hospitals five to ten years from now and thus obtain a quantitative measure of the effectiveness of the present policy of education.

SUMMARY

An analysis was made of data obtained in 581 cases of cutaneous carcinoma at the Collis P. Huntington Memorial Hospital.

The median size and the median duration were convenient measures of the stage of development of the cutaneous tumors in this group. The median duration of basal cell carcinoma (three and five-tenths years) was much greater than that of epidermoid carcinoma (one and two-tenths years). The median sizes of the two types of tumor were, however, the same (1.9 cm.).

It seemed that the size, not the duration of the tumor, prompted the average patient to seek hospital treatment.

At time of hospitalization the median age of patients was 64.2 years for those with basal cell carcinoma and 68.2 years for those with epidermoid carcinoma. At time of onset the median age for those with basal cell tumors was only 57.3 years, as compared with 66.2 years for those with epidermoid lesions. The basal cell tumors developed, therefore, in a much younger group of persons than the epidermoid ones (the difference in median ages was 8.9 years).

An analysis of data obtained in 495 cases of cutaneous carcinoma at Pondville Hospital added the following information:

The findings as to the differences in the median durations and the median ages at time of hospitalization and at time of onset were confirmed.

The patients of the Pondville Hospital were on the average somewhat older and had slightly larger lesions than the patients of Huntington Hospital.

CUTANEOUS CARCINOMA

II. A STATISTICAL ANALYSIS WITH RESPECT TO MEASURES OF INNATE AND CLINICAL MALIGNANCY

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Malignancy can be defined from the viewpoint of the pathologist and from that of the clinician.

Malignancy from the pathologist's viewpoint (or innate malignancy) is the degree of deviation of the tumor from its prototype. For instance, epidermoid carcinoma deviates from its prototype, squamous epithelium. Innate malignancy may be measured by (1) the anaplasia of the tumor cells, (2) the growth capacity of the tumor and (3) the capacity of the tumor for metastasis.

The degree of anaplasia of the tumor cells is the basis for Broder's measurement of malignancy.[1] This method is of theoretic interest and of clinical importance but is largely confined to comparison of tumors arising from a common prototype. It is not possible, for example, to compare, with respect to anaplasia, epidermoid carcinoma, basal cell carcinoma, adenocarcinoma and fibrosarcoma.

Casey [2] measured malignancy by means of the mitotic index. This is an indirect method of determining the growth capacity of a tumor. He found this method useful in comparing tumors diagnosed as lymphoma. Whether the mitotic count can be used to compare neoplasms arising from different prototypes is not clear from the available data. It is probable that factors other than the number of mitoses determine rapidity of growth.

Another method of determining the growth capacity is the use of the growth rate. This permits, it seems, a comparison of tumors arising from different protypes as to innate malignancy.

The frequency of metastasis is also a measure of innate malignancy. It must be pointed out, however, that factors other than innate malignancy determine the actual frequency of metastasis. Some of these

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1. Broders, A. C.: J. A. M. A. **74**:656, 1920.
2. Casey, A. E.: Am. J. Cancer **29**:47, 1937.

secondary factors are the character of the blood supply and the lymph drainage of the site of the tumor and the amount of trauma to which the tumor is subjected.

The malignancy of a tumor from the clinician's viewpoint (or clinical malignancy) is the hazard to the health and life of the patient. This hazard is dependent on a number of factors, the chief of which is usually innate malignancy. Location is also an important factor and is, in some cases, of paramount importance. Epidermoid carcinoma of the hand, the tongue and the esophagus may have the same innate malignancy but have widely diverse degrees of clinical malignancy. The type of therapeutic intervention is another factor.

Clinical malignancy is usually measured by the percentage of five year cures. It can also be measured by the duration of life in treated and untreated patients,[3] survival curves,[4] life expectancy curves,[5] percentage of patients with recurrences and percentage of patients dying with the malignant growth. If secondary factors, such as location, are maintained constant, the measurements of clinical malignancy are an index of innate malignancy.

In this study, the innate malignancy of basal cell and that of epidermoid carcinoma are measured by a growth index and by the percentage of tumors metastasizing. The clinical malignancy of these tumors is represented graphically by prognostic curves. In other words, this paper considers the growth, the prognosis and the efficacy of treatment of cutaneous tumors.

GROWTH INDEX AS A MEASURE OF INNATE MALIGNANCY

Although growth is one of the most important characteristics of neoplasms, little if any work, it seems, has been done on measuring and comparing the growth rates of human tumors. Clinicians have, however, obtained general impressions.[6] Certain tumors are known to increase in size rapidly, others slowly. Some tumors grow progressively; others are believed to have cycles of growth and quiescence. Some factors—pregnancy, menopause, age—are supposed to accelerate or to inhibit the development of certain tumors. The growth rate of the metastasis may, it is believed, be quite different from that of the primary tumor. These clinical impressions have not, however, been tested by quantitative methods.

The growth of animal tumors has been studied to some extent by Bashford,[7] Mayneord,[8] Schrek[9] and others. These workers agree that the growth rate is an important physiologic characteristic of a tumor.

3. Daland, E. M.: Surg., Gynec. & Obst. **44**:264, 1927.
4. Jacobs, L. G.: Radiology **27**:468, 1936.
5. Nathanson, I. T., and Welch, C. E.: Am. J. Cancer **28**:40, 1936.
6. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1928, p. 59.

The growth of human tumors could best be studied by periodic observation of untreated patients over a long stretch of time. This desideratum cannot, of course, be achieved except in some terminal cases and in a few isolated cases in which the patients refuse treatment. It was necessary, therefore, to resort to a statistical analysis of large numbers of tumors.

Method.—The growth index was defined as the ratio of the size at time of hospitalization to the duration of the tumor. The work of Mayneord [8] and Schrek [9] indicates that the maximum diameter or the mean diameter is the most satisfactory measure of size. For tumors of the human skin, the length or maximum diameter seemed the most convenient. The length of each tumor was determined by the clinician or the pathologist after excision. The duration of the lesion was taken from the anamnesis. A previous paper [10] discusses in detail the sources of error of the methods used in determining the length and duration of the individual tumor.

The data on the size and duration of epidermoid carcinoma of the lip were collected by Drs. Grantley W. Taylor and Ira T. Nathanson for another investigation. These investigators gave me permission to use their data.

The growth index for each tumor was calculated by dividing its greatest diameter in millimeters by its duration in months. Cumulative frequency curves for the growth indexes of the tumors were then constructed on logarithmic probability paper.[11]

Comparison of the Growth Indexes of Basal Cell and Epidermoid Carcinoma.—The cumulative frequency curves for the growth indexes of basal cell carcinoma and epidermoid carcinoma of the skin and of the lip are given in chart 1. The curves are rectilinear and represent therefore normal frequency distributions. The median growth indexes of epidermoid carcinoma of the lip and of the skin were approximately the same, 1.85 mm. per month; that of basal cell carcinoma of the skin was, however, only one third as great or 0.51 mm. per month. It seems, then, that epidermoid carcinoma of the skin and of the lip has the same innate malignancy but that basal cell carcinoma has considerably lower malignancy.

Although the median growth indexes of epidermoid carcinoma of the skin and of the lip are the same, the slope of the cumulative frequency curve for the labial tumors is less than that for the cutaneous lesions. This difference in slopes indicates that carcinoma of the lip varies less in regard to growth index than carcinoma of the skin. Tumors of the

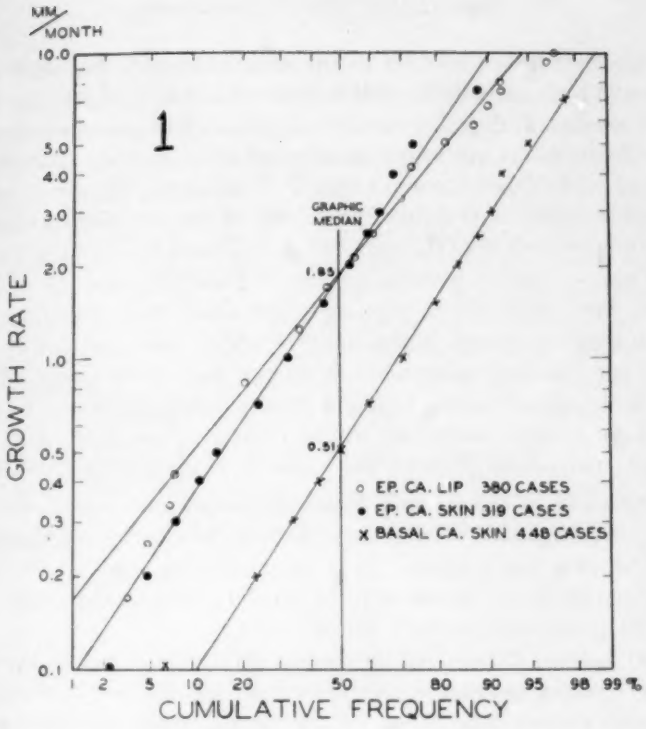
7. Bashford, E. F.: Scient. Rep. Invest. Imp. Cancer Research Fund **4**: 131, 1911.

8. Mayneord, W. V.: Am. J. Cancer **16**:841, 1932.

9. Schrek, R.: Am. J. Cancer **28**:345, 1936.

10. Schrek, R., and Gates, O.: Arch. Path., this issue, p. 411.

11. Schrek, R., and Lipson, H. I.: Human Biol. **13**:1, 1941.



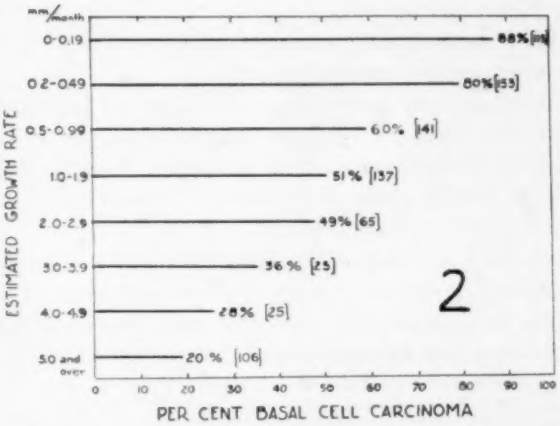


Chart 1.—Cumulative frequency curves of the growth indexes of cutaneous and labial epidermoid carcinoma and of cutaneous basal cell carcinoma. The median growth indexes of the epidermoid tumors of the skin and of the lip are the same, 1.85 mm. per month; the median index of the basal cell tumors is only 0.51 mm. The variability of the growth index of labial epidermoid carcinoma (as indicated by the slope of the curve) is less than that of cutaneous epidermoid carcinoma.

Chart 2.—The percentage of basal cell tumors according to the growth index.

skin with their wide variation in site may be expected to show greater variation in their growth rates than those of a restricted site, the lips.

The marked differences in the growth indexes of epidermoid and basal cell carcinoma are represented graphically in chart 2, constructed from data of the Pondville and Collis P. Huntington Memorial hospitals. It is evident from chart 2 that 88 per cent of the cutaneous tumors with growth indexes less than 0.2 mm. per month were basal cell in type. Of tumors having growth indexes between 0.2 and 0.5 mm. per month, 80 per cent were basal cell in type. On the other hand, rapidly growing carcinoma with a growth index of 5.0 or above was basal cell in type in only 20 per cent and epidermoid in 80 per cent of the cases. It seems that a cutaneous carcinoma having a growth index less than 0.5 mm. per month is in a large percentage of cases basal cell in type; if the index is 5.0 mm. per month or more, the tumor is in most cases epidermoid.

Comparison of the Growth Rates of Human and Rat Tumors.—In previous investigations [9] the growth rates of certain types of transplantable rat tumors was studied. It is of interest to compare the human tumors studied in this paper with the rat tumors previously studied with respect to growth rate (table 1 and chart 3).

Chart 3 shows clearly that the median growth rates for the rat tumors (Flexner-Jobling carcinoma, Walker carcinoma 256 and R39 sarcoma) were much greater than those for the human cutaneous tumors. The median growth rate of the rat tumors was approximately 0.5 to 2 mm. per *day*, whereas the median growth rate for the human tumors was about 0.5 to 2 mm. per *month*. In other words, the rat tumors grew about thirty times more rapidly than the human tumors. The rat tumors had, then, a much higher innate malignancy.

It is also evident from chart 3 that the slopes of the curves for the human tumors are much greater than those for the rat tumors. Since the slope is a graphic representation of variability, it seems that the measurements of the growth rates of the human tumors varied much more than those of the rat tumors.

To compare the variability of the different tumors quantitatively, the geometric standard deviations [11] were used as a measure of variability. These constants were determined from the graph represented in chart 3. The rat tumors had low geometric standard deviations (1.21, 1.30 and 1.31) whereas the corresponding constants for the human tumors were almost three times as much (2.79, 3.56 and 3.72). Evidently the growth rates of the cutaneous tumors of man varied much more than those of the rat tumors.

This great variability of the growth indexes of human tumors was presumably the result of (1) the greater error in the determination of these indexes, (2) the greater heterogeneity of the spontaneous human tumors as compared with the transplanted rodent tumors and (3) the greater variability of the human hosts.

Percentage of Tumors Metastasizing as a Measure of Innate Malignancy.—It is well known that epidermoid carcinoma has a tendency to metastasize to regional lymph nodes, whereas basal cell carcinoma rarely metastasizes. According to the data of Pondville Hospital, epidermoid

TABLE 1.—*A Comparison of Rat and Human Tumors with Respect to the Median Growth Rate and the Variability of the Growth Rate*

	Median Growth Rate *		Growth Rate of 90% of Tumors (90% Range)		Geometric Standard Deviation *
	Mm. per Month	Mm. per Day	Mm. per Month	Mm. per Day	
Rat tumors, transplantable					
R 39 sarcoma	....	1.77	.....	1.06-2.48	1.30
Walker carcinoma 256	....	1.22	.....	0.71-1.73	1.31
Flexner-Jobling carcinoma	....	0.65	.....	0.45-0.85	1.21
Human tumors, spontaneous					
Basal carcinoma of skin	0.51	....	0.06- 4.5	.....	3.72
Epidermoid carcinoma of skin	1.85	....	0.23-15.0	.....	3.56
Epidermoid carcinoma of lip	1.85	....	0.36-10.5	.....	2.79

* The value was determined from chart 3.

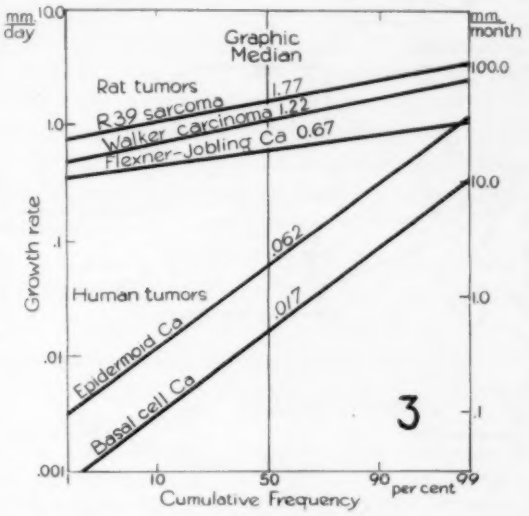


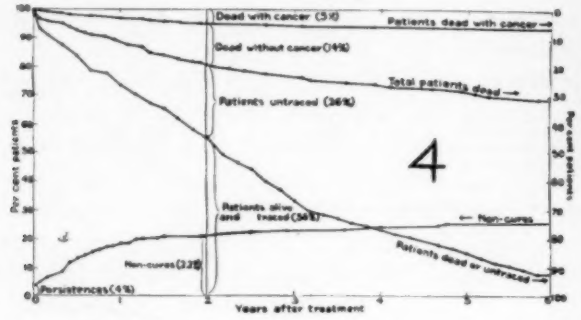
Chart 3.—A comparison of the cumulative frequency curves of the growth rates of transmissible rat tumors and cutaneous tumors of man. The median growth rates of the human neoplasms are much less than those of the rat tumors. The variability of the growth rates of the two types of human carcinomas (as measured by the slopes of the curves) is greater than that of the three types of rat tumors.

carcinoma metastasized in 17.1 per cent of the 198 cases. In contrast only 1 (0.3 per cent) of the 300 tumors diagnosed as basal cell carcinoma was observed to give rise to metastatic nodes. This metastasis occurred in a case of mixed basal cell and epidermoid carcinoma, and it was the epidermoid portion that metastasized. These observations agree with those of other workers.

With the percentage of tumors metastasizing as a measure of innate malignancy, it seems that basal cell carcinoma has a much lower degree of malignancy than epidermoid carcinoma.

PROGNOSTIC CURVES AS MEASURES OF CLINICAL MALIGNANCY

To determine the results of treatment of carcinoma, it is necessary that a large group of patients should be observed at regular intervals for a sufficiently long period. Pondville Hospital maintains very satis-



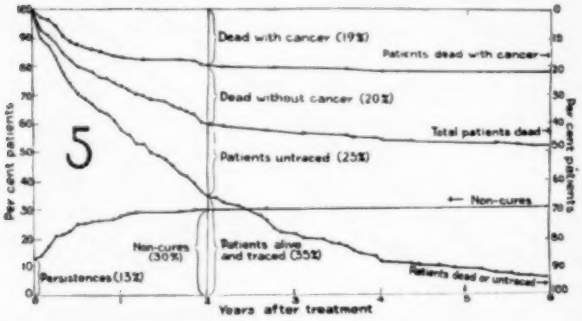


Chart 4.—Prognostic curves of 298 patients with basal cell carcinoma. The curves show what happened to the patients and to the tumors during a five year period following treatment. Only 4 per cent showed persistence of their tumors. During the first two years after treatment, 5 per cent of the patients died with carcinoma, 13 per cent died free from carcinoma, 26 per cent were not traced, and 18 per cent of the patients had recurrences.

Chart 5.—Prognostic curves of 197 patients with epidermoid carcinoma. The curves in this and in chart 4 show interesting similarities and differences. A detailed comparison of the various curves for epidermoid and basal cell carcinoma is given in charts 5 to 8.

factory follow-up contact with patients who have been treated for cancer, despite the great distances of many of the patients' homes from the hospital and in spite of the indifferent attitude of many patients with

cutaneous carcinoma. The social service department of the hospital is active in keeping in touch with each person whose condition has been diagnosed as malignant.

Patients entering this hospital up to Jan. 1, 1937 were included in this survey. Those entering more recently were, of course, followed up for only a short time.

Comprehensive Prognostic Curves.—A graphic and comprehensive method of representing the prognosis of a given type of tumor is given in chart 4 for basal cell carcinoma and in chart 5 for epidermoid carcinoma. These graphs show the results observed in Pondville Hospital following the first series of treatments in 298 cases of basal cell and 197 cases of epidermoid carcinoma. The treatments consisted of irradiation or surgical removal or both and were considered adequate except in a few cases in which the treatment was palliative. The patients in whom tumors recurred received subsequent treatment, and many of them were ultimately cured.

Charts 4 and 5 give a bird's eye view of what happens to the patients and to the tumors following treatment. The graph shows for any given time up to six years (1) the percentage of patients dying with carcinoma, (2) the percentage of patients dying without carcinoma, (3) the percentage of patients untraced, (4) the percentage with persistence of carcinoma and (5) the percentage with recurrence of carcinoma.

To compare the two figures in detail, it is necessary to construct supplementary graphs.

Percentage of Patients Dying with Carcinoma.—Chart 6 shows the percentage of patients who died with persistent or recurrent carcinoma. No attempt was made to differentiate between those dying from tumor and those dying from other causes but having incidentally cutaneous carcinoma. Both types of patients were included in the group of "Dead with Carcinoma."

It can be seen from chart 6 that few of the patients (only 5.7 per cent) were known to have died with persistent or recurrent basal cell carcinoma in the five years after the first series of treatments. Most of the patients died within the first eighteen months, but a few died as late as the third and fourth year.

In contrast, the percentage of patients dying with epidermoid carcinoma was much greater, 21.3 per cent for the five year period, as compared with 5.7 per cent for those with basal cell carcinoma. The difference is statistically significant.

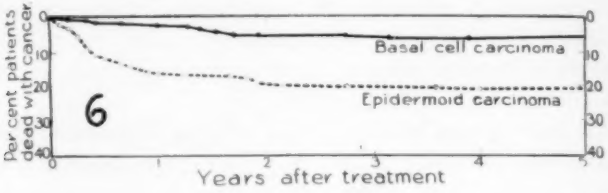
Most of the patients who died with an epidermoid lesion did so during the first twelve months after treatment, but a few died during the second and early part of the third year.

It is definite that the percentage of patients dying with epidermoid carcinoma was greater than that of patients dying with basal cell car-

cinoma. It seems, then, that the epidermoid tumors have not only a higher innate malignancy but also a higher clinical malignancy.

Percentage of Patients Dying Without Carcinoma.—In chart 7 is shown the percentage of patients who died without carcinoma. In the five years after treatment 22.5 per cent of the patients with basal cell carcinoma and 24.4 per cent of those with epidermoid carcinoma died free from cutaneous carcinoma. These percentages are high, but this is not surprising if one considers the advanced age of the patients with cutaneous carcinoma.

The percentage of patients who died without recurrent or persistent epidermoid carcinoma was somewhat higher than that for patients with



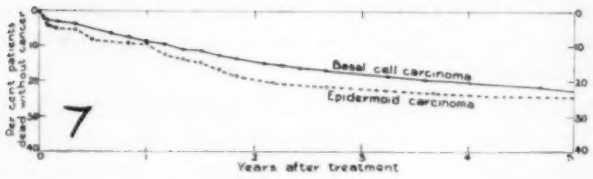


Chart 6.—A comparison of the percentages of patients who died with persistent or with recurring carcinoma. Few patients died with basal cell carcinoma. A greater percentage of patients died with epidermoid than with basal cell carcinoma. The differences in the percentages for the two types of tumors are statistically significant.

Chart 7.—A comparison of the percentages of patients who died free from the two types of cutaneous carcinoma. A considerable percentage of patients died free from tumor. There are slight, statistically insignificant differences in the percentages of the two series.

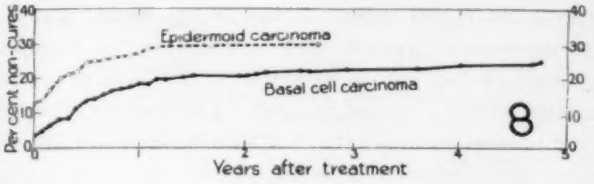
basal cell tumors. The differences are not statistically significant according to the monogram described by Schrek.[12] The slightly higher percentage for epidermoid carcinoma is associated with the higher median age of patients with this type of tumor.[11]

Percentage of Tumors Persisting.—Chart 8 shows that 12.7 per cent of the epidermoid and only 3.7 per cent of the basal cell tumors persisted

12. Schrek, R.: J. Lab. & Clin. Med. **25**:180, 1939.

after treatment. The difference, 9.0 per cent, is statistically significant. This finding is in agreement with the other observations that basal cell carcinoma has a lower grade of malignancy.

Percentage of Tumors Recurring.—The percental recurrences of the two types of cutaneous carcinoma are represented in chart 9. It is seen that for the first two years the two types of carcinoma had approximately the same percentage of recurrences. During the following three years the percentage of recurrences of basal cell carcinoma was slightly higher than that of epidermoid carcinoma. At the end of five years 21.5 per cent of the basal cell and only 17.8 per cent of the epidermoid tumors had recurred. The slight difference is not statistically significant.



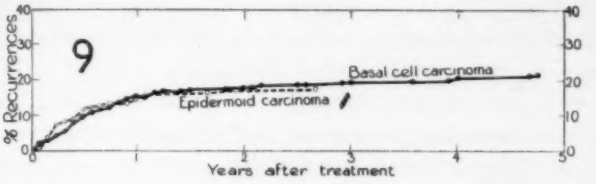


Chart 8.—A comparison of the percentages of patients without cures following treatment for the two types of cutaneous carcinoma. The curves show the percentages of patients whose tumors persisted or recurred. Only few basal cell but many epidermoid tumors persisted after treatment. The percentage of noncures of epidermoid tumors is much greater than that of noncures of basal cell tumors.

Chart 9.—A comparison of the percentages of patients with recurrences following treatment for the two types of cutaneous carcinoma. The two types of tumors recurred in approximately the same percentage of patients.

COMMENT

The concepts of innate and clinical malignancy were defined in the introduction of this paper. Now it is necessary to consider the significance of the methods used in measuring malignancy, i. e., the growth index and the prognostic curves.

Growth Index.—In previous studies on rat transplantable tumors the growth rate was found useful in comparing different tumors as to innate

malignancy,[9] in comparing malignant and embryonic growth,[13] and in measuring the effect of various factors on tumor growth.[14]

In the present study on two types of spontaneous cutaneous carcinoma in man the growth index not only is of theoretic interest but has in addition an immediate practical use. It has been shown that the growth index of epidermoid carcinoma is considerably greater than that of basal cell carcinoma. This difference can be used to aid in the clinical differentiation of the two types of carcinoma.

The growth index has another practical application; it may facilitate the study of the effects of therapeutic agents on human tumors. It appears that a delicate test for the determination of the value of a possible therapeutic agent would be the effect of the agent on the growth rate. A decrease of growth rate should be apparent before regression of the tumor, and if the agent failed to cause regression but did produce appreciable decrease in growth rate, it would be of therapeutic value. But before such studies can be undertaken, the normal growth rates of human tumors have to be determined. To conclude, the effect of an agent on the normal growth rate of a tumor should be an accurate test of the therapeutic effectiveness of that agent.

Prognostic Curves.—The representation of the various possibilities that may follow the treatment of carcinoma necessitates a comprehensive prognostic chart, as shown in charts 4 and 5. Such a chart summarizes in compact form the actual observations and does not depend on any assumptions in regard to time when the patient is cured or in regard to the number of cures in untraced patients. From these prognostic charts, the reader can determine for himself any particular constant he may be interested in. Furthermore, the graphs suggest which time intervals are significant.

Three measures of clinical malignancy can be derived from the prognostic charts: percentage of patients dying with carcinoma, percentage with persistence of carcinoma, and percentage with recurrence. These percentages may be taken at any time interval. The two and four year intervals seem to be of particular interest.

Malignancy of Basal Cell and Epidermoid Carcinoma.—In table 2 are summarized the measurements of the innate and clinical malignancy of the two types of cutaneous carcinoma. It can be seen that basal cell carcinoma is only about one-third as malignant as epidermoid carcinoma, according to the growth index, the percentage of persons dying with carcinoma and the percentage of patients with persistence. The percentage with recurrence of basal cell carcinoma is, however, surprisingly high (21.5 per cent); in fact, slightly higher than that for epidermoid carcinoma (17.6 per cent).

13. Schrek, R.: Am. J. Path. **12**:525, 1936.
14. Schrek, R.: Am. J. Cancer **28**:364, 1936.

One factor that may be responsible for the relatively high percentage of patients with recurrence of basal cell carcinoma is the difference in the sites of predilection of the two types of carcinoma. The basal cell type prefers the upper part of the face and the nose while the epidermoid type shows a preference for the ear and hand.[15] Since any tumor of the upper part of the face or of the nose is more difficult to treat radically, basal cell carcinoma would be expected to show less satisfactory results than epidermoid carcinoma.

The conservatism of surgeons and radiologists in treating basal cell carcinoma may be another factor responsible for the high percentage of patients with recurrence of basal cell carcinoma. This conservatism in treatment is presumably due to the desire to obtain a good plastic result and the knowledge that carcinoma of this type has low malignancy. In view of the high percentage of patients with recurrence and since the

TABLE 2.—*A Comparison of Cutaneous Basal Cell and Epidermoid Carcinoma as to Innate and Clinical Malignancy*

	Basal Cell Carcinoma	Epidermoid Carcinoma
Innate malignancy		
Growth index (mm. per month)	0.51 (448)*	1.85 (319)*
Percentage of patients with metastasis	0.3 (298)	17.1 (198)
Clinical malignancy		
Percentage of patients dying with carcinoma—five years	5.7 (298)	21.8 (198)
Percentage with persistence	3.7 (298)	12.6 (198)
Percentage with recurrence	21.5 (298)	17.6 (198)
Percentage without cures	25.2 (298)	30.2 (198)

* The numbers in parentheses indicate the number of cases on which the statistic is based.

recurrent tumors are more difficult to treat than the primary tumors,[15] it appears that conservative treatment of basal cell carcinoma is not always wise.

SUMMARY

Tumors have two distinct types of malignancy—innate and clinical malignancy. The innate malignancy of a neoplasm is the degree of deviation of the tumor from the prototype. Clinical malignancy is the hazard of the tumor to the life and health of the patient.

The innate malignancy of epidermoid and basal cell carcinoma of the skin was measured by the median growth rate and the percentage of tumors metastasizing. The clinical malignancy of these tumor types was represented graphically by prognostic curves and was measured by percentage of patients dying with the carcinoma, the percentage with persistence and the percentage with recurrence.

Most of these measures of innate and clinical malignancy agree in indicating that epidermoid carcinoma is about three times as malignant as basal cell carcinoma. However, in spite of its low malignancy, the basal cell type recurs in as high a percentage of cases as the epidermoid type.

15. Schrek, R.: Arch. Path., this issue, p. 434.

CUTANEOUS CARCINOMA

III. A STATISTICAL ANALYSIS WITH RESPECT TO SITE, SEX AND PREEXISTING SCARS

ROBERT SCHREK, M.D.
HINES, ILL.

In previous papers [1] there was presented an analysis of the characteristics of cutaneous carcinoma as a whole. In this report the tumors of the various regions of the skin are considered separately. The sites were classified in accordance with the work of Warren, Gates and Butterfield.[2]

ALL SITES

The cases used in this analysis comprise 1,231 of basal cell and 856 of epidermoid carcinoma from the Massachusetts Diagnostic Service and 296 of basal cell and 197 of epidermoid carcinoma from Pondville Hospital (table 1a).

Of the tumors that occurred in males, 55 per cent (Massachusetts Diagnostic Service) and 56 per cent (Pondville Hospital) were basal cell in type. The corresponding percentages for the tumors occurring in females were 66 and 70 per cent.

Of the patients with epidermoid carcinoma, 67 and 78 per cent were males (table 1a) while, of those with basal cell carcinoma, 57 and 68 per cent, respectively, were males. Males, then, appear to have a greater predisposition to both types of tumors, particularly the former, than females.

A small proportion of the patients gave a definite history of the tumor developing on the basis of an old scar and in most of them the scar was still visible at the time of admission to the hospital. Table 2 shows that in 5 instances (3.4 per cent) basal cell and in 9 (5.1 per cent) epidermoid carcinoma developed in scars. The difference in the percentages is not sufficiently marked to be statistically significant ($P = 0.6$).

From the laboratories of pathology of Pondville Hospital, Wrentham, Mass., and the Collis P. Huntington Memorial Hospital, Boston.

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1. Schrek, R., and Gates, O.: Arch. Path., this issue, p. 411. Schrek, R.: ibid., this issue, p. 422.

2. Warren, S.; Gates, O., and Butterfield, P. W.: New England J. Med. **215**: 1060, 1936.

Metastasis to neighboring lymph nodes was observed in only 32, or 16 per cent, of the 197 cases of epidermoid carcinoma of Pondville Hospital (table 3).

UPPER PART OF FACE

In many of the cases of cutaneous carcinoma the growth developed on the upper part of the face (table 1a). In the series of the Massachusetts Diagnostic Service, basal cell carcinoma occurred on the upper part of the face in 30.0 per cent and epidermoid carcinoma in 16.8 per cent of the cases. The corresponding figures for Pondville Hospital were 44.6 and 30.0 per cent. Many of the cases of the diagnostic service were not used in this table as the records failed to specify definitely whether the tumor occurred on the upper or on the lower part of the face. The omission of these cases accounts for the relatively low percentages for the diagnostic service. Probably the percentages given for Pondville Hospital are more accurate in spite of the fewer cases in this series.

In about 70 per cent of the cases in which the carcinoma occurred on the upper part of the face it was basal cell in type. This site has, then, a definitely more marked predisposition for basal cell than for epidermoid carcinoma.

Table 1a shows also the relative numbers of males and females in whom carcinoma developed on the upper part of the face. Of the tumors observed at this site in the Massachusetts Diagnostic Service, 55 per cent occurred in males; of those observed in Pondville Hospital, 67 per cent occurred in males. Evidently more males than females have cutaneous carcinoma at this site.

Although many patients of Pondville Hospital gave a history of previous injury, only in 1 of the 191 cases of tumor of the upper part of the face (0.5 per cent, table 2) did the growth arise definitely in a preexisting scar. This was a tumor of seven years' duration, diagnosed as basal cell carcinoma, that developed on the forehead of a 76 year old woman. The patient gave a history of a burn occurring twenty to twenty-five years prior to hospitalization. The injury resulted in a well healed scar, which ulcerated about thirteen to eighteen years afterward.

Forehead.—Twenty-one patients of Pondville Hospital had cutaneous carcinoma of the forehead (table 1a). Of these 18, or 86 per cent, had basal cell and only 3 had epidermoid carcinoma. Of the 296 basal cell tumors of Pondville Hospital, 6.1 per cent occurred on the forehead, while only 1.5 per cent of all the epidermoid tumors developed in this site. It seems from these statistics that the skin of the forehead has a greater predilection for basal cell carcinoma.

Table 1a shows, furthermore, that 8, or 38 per cent, of the 21 tumors occurred in male patients. More females than males, therefore, had cutaneous carcinoma at this site.

Eyelids and Canthi.—The lids and canthi of the eyes were found to have cutaneous carcinoma in 30 cases (table 1a). Most of the tumors occurred either on the inner canthi or on the lower lids. Only 5 tumors were observed on the upper lids and in the outer canthi.

In 26 of the 30 cases (87 per cent) the tumors of these sites were basal cell in type. Furthermore, 8.8 per cent of all the cutaneous basal cell tumors, but only 2.0 per cent of all the epidermoid tumors, occurred on the eyelids and canthi. These sites, then, like the forehead, have a marked preference for basal cell carcinoma.

Of the 30 patients in this group, 19, or 63 per cent, were males.

Upper Lip.—There were 27 patients with carcinoma of the skin of the upper lip. Of these, 67 per cent were males. Most of the tumors (89 per cent of 27) were diagnosed as basal cell carcinoma.

Cheek.—In a large number of the cases of cutaneous carcinoma (78, or 16 per cent of all) the tumor occurred on the cheek. Carcinoma at this site was found most frequently in males (67 per cent), and in only 56 per cent of the cases was it basal cell in type. The skin of the cheek, unlike that of the forehead, eyelids and upper lip, does not show any definite predilection for basal cell carcinoma.

Temporal-Zygomatic Regions.—In 32 cases the cutaneous carcinoma occurred in the temporal-zygomatic region. In only 53 per cent of these was it of the basal cell type. Eighty-eight per cent of the patients were males. This site like the cheek did not have any preference for either type of carcinoma, but an excess of males had cutaneous carcinoma of this region.

NOSE

The skin of the nose is a favorite site for carcinoma; it was involved in about 20 per cent of the cases of basal cell and 10 per cent of the cases of epidermoid carcinoma (table 1b). These percentages take on added significance when one considers that the skin of the nose is only a small fraction of the total surface of the body. Table 1b shows, furthermore, that in a high proportion (73 and 81 per cent) of the cases the carcinoma was basal cell in type. It seems, then, that the skin of the nose has a marked predisposition for basal cell carcinoma.

The percentages of males with this site involved were 59 and 69 for the two series.

The cases of Pondville Hospital were classified according to the part of the nose affected, the nose being subdivided into bridge, alae, tip and lower edge. In most of the cases the tumor occurred on the alae. In 15 instances the bridge of the nose was involved and in 80 per cent of these the carcinoma was basal cell in type; in 11 cases the tip was involved, and in all the carcinoma were of the basal cell type. Although the series are small, it seems that the bridge and tip of the nose were the sites of basal cell carcinoma in particularly high percentages.

TABLE 1a.—*An Analysis of the Incidence of Cutaneous Carcinoma According to Site, Sex and Type of Tumor (Massachusetts Diagnostic Service and Pondville Hospital Series)*

Site	Cases *							Percentage of Cases †		Percentage of Cases of Basal Cell Carcinoma ‡			Percentage of Males §		
	Basal Cell Carcinoma			Epidermoid Carcinoma											
	M	F	Total	M	F	Total	Total	B	E	M	F	Total	B	E	Total
	a	b	c = a + b	d	e	f = d + e	g = c + f	h = c / Total	i = f / Total	j = a / a + d	k = b / b + e	l = c / g	m = a / c	n = d / f	o = a + d / g
All sites:															
Mass. Diagnostic Service	700	531	1,231	577	279	856	2,087	100	100	55	66	59	57	67	61
Pondville Hospital.....	195	101	296	153	44	197	493	100	100	56	70	60	66	78	71
Upper part of face:															
Mass. Diagnostic Service	194	175	369	86	58	144	513	30.0	16.8	69	75	72	53	60	55
Pondville Hospital.....	86	46	132	42	17	59	191	44.6	30.0	67	73	69	65	71	67
Forehead.....	8	10	18	0	3	3	21	6.1	1.5	100	77	86	44	0	38
Eyelids.....	16	10	26	3	1	4	30	8.8	2.0	84	91	87	62	75	63
Inner canthus.....	8	2	10	2	1	3	13								
Lower lid.....	4	6	10	0	0	0	10								
Upper lid.....	1	1	2	1	0	1	3								
Outer canthus.....	1	1	2	0	0	0	2								
Unspecified.....	2	0	2	0	0	0	2								
Upper lid.....	17	7	24	1	2	3	27	8.1	1.5	94	78	89	71	33	67
Central.....	8	4	12	1	2	3	15								
Nasolabial.....	9	3	12	0	0	0	12								
Cheek.....	28	16	44	24	10	34	78	14.9	17.2	54	62	56	64	71	67
Near nose.....	7	5	12	1	0	1	13								
Malar.....	8	6	14	7	4	11	25								
Preauricular.....	12	4	16	11	2	13	29								
Unspecified.....	1	1	2	5	4	9	11								
Temporal-zygomatic...	14	3	17	14	1	15	32	5.7	7.6	50	75	53	82	93	88
Unspecified.....	3	0	3	0	0	0	3								

* The abbreviations used in this table are: M, male; F, female; B, basal cell carcinoma; E, epidermoid carcinoma.

† Percentage of cases = number of cases of tumor (basal cell or epidermoid) in particular site divided by total number of cases of tumor (basal cell or epidermoid) in whole series.

‡ Percentage of cases of basal cell carcinoma = number of cases of basal cell carcinoma in particular site (for M, F or both) divided by total number of all cases of carcinoma (basal cell plus epidermoid) in particular site (for M, F or both).

§ Percentage of males = number of tumors (basal cell or epidermoid) in particular site occurring in males divided by number of tumors (basal cell or epidermoid) in particular site occurring in both sexes.

TABLE 1b.—*An Analysis of the Incidence of Cutaneous Carcinoma According to Site, Sex and Type of Tumor (Massachusetts Diagnostic Service and Pondville Hospital Series)*

Site	Cases							Percentage of Cases		Percentage of Cases of Basal Cell Carcinoma			Percentage of Males		
	Basal Cell Carcinoma			Epidermoid Carcinoma											
	M	F	Total	M	F	Total	Total	B	E	M	F	Total	B	E	Total
Nose:															
Mass. Diagnostic Service	139	93	232	50	38	88	320	18.8	10.3	74	71	73	60	57	59
Pondville Hospital	44	19	63	10	5	15	78	21.3	7.6	82	79	81	70	67	69
Bridge	8	4	12	2	1	3	15	....	....	80	80	80			
Alae	19	10	29	6	4	10	39	....	....	76	71	74			
Tip	8	3	11	0	0	0	11	....	....	100	100	100			
Edge	3	0	3	1	0	1	4								
Unspecified	6	2	8	1	0	1	9								
Lower face:															
Mass. Diagnostic Service	102	69	171	52	21	73	244	13.9	8.5	66	77	70	60	71	63
Pondville Hospital	13	7	20	6	2	8	28	6.8	4.1	68	78	71	65	75	68
Chin	3	3	6	1	1	2	8								
Mandible	10	4	14	5	1	6	20								
Ear:															
Mass. Diagnostic Service	134	59	193	184	25	209	402	15.6	24.4	42	70	48	69	88	79
Pondville Hospital	27	6	33	41	8	43	76	11.2	21.8	40	75	43	82	95	90
Anterior	5	3	8	9	2	11	19								
Helix	7	2	9	8	0	8	17								
Posterior	5	0	5	3	0	3	8								
Mastoid	9	0	9	4	0	4	13								
Unspecified	1	1	2	17	0	17	19								
Scalp:															
Mass. Diagnostic Service	15	21	36	7	14	21	57	2.9	2.5	68	60	63	42	33	39
Pondville Hospital	3	6	9	2	1	3	12	3.0	1.5	60	86	75	33	67	42

TABLE 1c.—*An Analysis of the Incidence of Cutaneous Carcinoma According to Site, Sex and Type of Tumor (Massachusetts Diagnostic Service and Pondville Hospital Series)*

Site	Cases							Percentage of Cases		Percentage of Cases of Basal Cell Carcinoma			Percentage of Males		
	Basal Cell Carcinoma			Epidermoid Carcinoma											
	M	F	Total	M	F	Total	Total	B	E	M	F	Total	B	E	Total
Neck:															
Mass. Diagnostic Service	47	29	76	40	14	54	130	6.2	6.3	54	68	58	62	74	67
Pondville Hospital.....	3	8	11	11	1	12	23	3.7	6.1	21	89	48	27	92	61
Anterior.....	0	0	0	0	1	1	1								
Lateral.....	3	4	7	10	0	10	17								
Posterior.....	0	4	4	1	0	1	5								
Trunk:															
Mass. Diagnostic Service	37	51	88	21	40	61	149	7.2	7.1	64	56	59	42	34	39
Pondville Hospital.....	12	3	15	3	4	7	22	5.1	3.6	80	43	68	80	43	68
Anterior.....	1	0	1	2	3	5	6	...	...	..	..	17			
Posterior.....	11	3	14	1	1	2	16	...	...	..	..	87			
Arm:															
Mass. Diagnostic Service	9	8	17	14	10	24	41	1.4	2.8	39	44	41	53	58	56
Pondville Hospital.....	4	1	5	6	4	10	15	1.7	5.1	40	20	33	80	60	67
Leg:															
Mass. Diagnostic Service	9	13	22	9	12	21	43	1.8	2.5	50	52	51	41	43	42
Pondville Hospital.....	1	3	4	6	1	7	11	1.4	3.6	14	75	36	25	86	64
Hand:															
Mass. Diagnostic Service	14	12	26	108	44	152	178	2.1	17.8	11	21	15	54	71	69
Pondville Hospital.....	2	2	4	25	7	32	36	1.4	16.2	7	22	11	50	78	75
Dorsum.....	1	1	2	20	6	26	28								
Palm.....	0	1	1	1	0	1	2								
Thumb and fingers.....	1	0	1	3	0	3	4								
Unspecified.....	0	0	0	1	1	2	2								
Foot:															
Mass. Diagnostic Service	0	1	1	6	3	9	10	0.1	1.1	0	25	10	0	67	60
Pondville Hospital.....	0	0	0	1	0	1	1	0.0	0.5						

In 1 of the 78 cases (1.3 per cent) the carcinoma developed in a scar (table 2). In 4 of the 15 cases of epidermoid carcinoma of the nose (27 per cent) the neoplasm metastasized to regional lymph nodes (table 3).

TABLE 2.—*The Numbers and Percentages of Tumors Developing from Preexisting Scars (Pondville Hospital Series)*

	Basal Cell Carcinoma		Epidermoid Carcinoma		Both Types of Carcinoma		
Site	Tumors	Pre-existing Scars	Tumors	Pre-existing Scars	Tumors	Pre-existing Scars	Percentage of Tumors Arising in Preexisting Scars
All sites:							
Males	195	2	153	6	348	8	2.3
Females	101	3	44	3	145	6	4.1
Total	296	5	197	9	493	14	2.8
Upper part of face	132	1	59	0	191	1	0.5
Nose	63	1	15	0	78	1	1.3
Lower part of face	20	0	8	0	28	0	0.0
Ear	33	0	43	0	76	0	0.0
Scalp	9	1	3	1	12	2	16.7
Neck	11	0	12	0	23	0	0.0
Trunk	15	0	7	2	22	2	9.1
Arm	5	0	10	2	15	2	13.3
Leg	4	1	7	4	11	5	44.4
Hand	4	1	32	0	36	1	2.8
Foot	0	0	1	0	1	0	0.0

TABLE 3.—*The Numbers and Percentages of Epidermoid Tumors That Metastasized to Regional Lymph Nodes (Pondville Hospital Series)*

		Metastases			Percentage of Tumors Giving Rise to Metastases
Site	Epidermoid Tumors	At Time of Hospitalization	After Hospitalization	Total	
All sites	197	10	22	32	16
Upper part of face	59	4	8	12	20
Nose	15	0	4	4	27
Lower part of face	8	1	0	1	
Ear	43	2	4	6	14
Scalp	3	0	0	0	
Neck	12	0	0	0	0
Trunk	7	0	0	0	
Arm	10	2	1	3	30
Leg	7	0	0	0	
Hand	32	0	5	5	16
Foot	1	1	0	1	

LOWER PART OF THE FACE

The percentages of cases of cutaneous carcinoma involving the lower part of the face showed some discrepancies in the two series (table 1b). For reasons already stated, the figures for the Pondville Hospital are considered more reliable. In only 6.8 per cent of the cases of basal cell and 4.1 per cent of those of epidermoid carcinoma at Pondville Hospital was the growth localized on the lower part of the face. The nose

in comparison was involved in two to three times as many cases (21.3 and 7.6 per cent). In a fairly high proportion of the cases in which this site was involved (68 per cent) the tumor was basal cell carcinoma. The lower part of the face, then, was not as frequently affected by carcinoma as the upper part of the face and the nose. Of the tumors that did occur on the lower site, a great majority were diagnosed as basal cell carcinoma.

More than one half of the patients in this group were males (63 and 68 per cent males). None of the tumors was reported developing on the basis of a scar. One of the 8 tumors diagnosed as epidermoid carcinoma metastasized (table 3).

EAR

Table 1b shows that almost one fourth of the epidermoid tumors and about one eighth of the basal cell tumors developed on ears or over mastoid regions. A high proportion (70 and 75 per cent) of the aural tumors in the females were diagnosed as basal cell carcinoma, but only 48 and 43 per cent of those in the males were of this type. It can also be seen from the table that the percentages of males with carcinoma at this site were 88 and 95 for epidermoid and 69 and 82 for basal cell carcinoma. These statistics indicate that the male was much more prone to have carcinoma of the ear than the female.

The difference of the sexes in the development of carcinoma of the ear might be explained by hypothecating some factor that causes epidermoid carcinoma in an unusually high number of males. This factor might be trauma, but table 2 shows that none of the 76 persons with carcinoma of the ear gave a good history of a preexisting scar. Further study of the protocols indicated, however, that 4 patients (3 males and 1 female) with epidermoid carcinoma (or 9 per cent) gave a history of frostbite of the ears. The interval of time between the injury and the neoplasm was eight months, ten months, ten years and thirty years. In contrast, none of 33 patients with basal cell carcinoma gave a history of frostbite. Whether the injury had anything to do with the development of the tumor in any instance cannot be stated definitely. The possibility that this factor is an etiologic agent should, however, be borne in mind in taking a history and in comparing statistics of countries with different climatic conditions.

Metastasis of epidermoid carcinoma of the ear occurred in 14 per cent of the cases.

SCALP

Table 1b shows that the scalp was involved in only 2 to 3 per cent of the cases of cutaneous carcinoma. In most of these cases (about 70 per cent), as in those in which the upper and lower parts of the face were involved, the carcinoma was basal cell in type. It is also evident

from the table that only 39 and 42 per cent of the patients in this group were males. In this respect, the group is similar to that of patients with carcinoma of the forehead, in which also there was a low percentage of males.

Two of the 12 tumors of this site, or 16.7 per cent, developed in preexisting scars. Both of these "scar tumors" occurred in females. One of the patients stated that the scar was due to a burn by a curling iron. The other patient suffered an avulsion of the scalp at the age of 14, when her hair caught in a wringing machine. The wound healed with the formation of an extensive scar. Thirty years later there developed at the vertex of the scalp a lesion which proved to be basal cell carcinoma.

A review of some of the cases of the Collis P. Huntington Memorial Hospital showed 8 tumors of the scalp, and 2 (25 per cent) of these developed in preexisting scars. One tumor, diagnosed as mixed basal cell and epidermoid carcinoma, developed in a 56 year old man fourteen years after a severe burn. The other tumor, diagnosed as epidermoid carcinoma, occurred in a woman 82 years old. At the age of 33, this woman had caught her hair in machinery, and the top of the scalp had been torn off. The tumor was first observed in the scar forty-seven years after the accident.

None of the three epidermoid tumors of the scalp metastasized, although the tumors were of large size and long duration.

NECK

The neck was the site in about 6 per cent of the cases of cutaneous carcinoma (table 1c). The tumor was basal cell carcinoma in about one half of the cases. About two thirds of the patients were males. None of the tumors developed in scars (table 2).

TRUNK

In spite of the large surface of the trunk, it was the site of cutaneous carcinoma in relatively few of the cases (4 to 7 per cent of all, as shown in table 1c). It should be noted that cases of carcinoma of the genitalia and of the mucocutaneous junction of the anus were not included in this study. The tumors of the trunk were mostly basal cell in type (59 per cent and 68 per cent).

Of the 149 tumors of the Massachusetts Diagnostic Service, only 39 per cent occurred in males. The percentage of males in the series of Pondville Hospital was much higher (68), but this finding has to be discounted as the series was quite small (22 cases). It seems that females tend to have carcinoma of the trunk more frequently than males.

Table 1c shows, furthermore, that only 1 (17 per cent) of the 6 tumors that developed on the anterior part of the chest was basal cell

carcinoma. In contrast, of the 16 tumors of the posterior surface of the trunk, 14, or 87 per cent, were basal cell in type. The two series are small, but the differences are sufficiently marked to be statistically significant. It follows, then, that the anterior surface of the trunk seems to have a predilection for epidermoid carcinoma, and the posterior surface, for basal cell carcinoma.

Two of the 22 tumors of this site (9 per cent, table 2) developed from scars. Both of these tumors were diagnosed as epidermoid carcinoma and occurred in male patients. In the first instance, a 5 year old boy received a severe burn of the anterior surface of the chest, resulting in an extensive healed scar. Fifty-nine years later the scar broke down with the formation of an ulcer, diagnosed, a year later, as epidermoid carcinoma. In the second, a boy received a severe burn of the scapular region with extensive scarring, which never healed completely but continued to give rise to superficial crusts. When the patient attained the age of 73, a progressively growing ulcer developed in the scar, and this lesion was diagnosed as epidermoid carcinoma two years later.

ARMS

The arms were the site of carcinoma in about 2 per cent of the cases. Of the tumors on the arms, only 30 to 41 per cent were basal cell in type. Most of the patients with tumors on this site were males (56 to 64 per cent).

Two of the 15 tumors of Pondville Hospital (13 per cent) developed from preexisting scars. The two tumors occurred in males and were diagnosed as epidermoid carcinoma. The scars were the result of burns.

Of 10 epidermoid tumors of the arm, 3, or 30 per cent, metastasized to regional lymph nodes.

LEGS

The legs were the site of about the same number of tumors as the arms, 2 to 4 per cent of all the tumors occurring on the legs (table 1c). According to the data from the Massachusetts Diagnostic Service, about one half of the tumors (51 per cent) were basal cell in type and less than one half of the tumors (42 per cent) developed in males. The leg is one of the few sites that showed a preponderance of tumors in females.

A high percentage of the tumors of the legs (5 of 11, or 45 per cent) arose in preexisting scars (table 2). These tumors included 1 of basal cell and 1 epidermoid type in females and 3 of epidermoid type in males. The basal cell tumor developed in a 73 year old woman who had scars following roentgen ray burns. One epidermoid tumor occurred on the leg of a 73 year old woman, at the site of a healed scar which had been present since childhood. The cause of the scar was not specified in the history. Another of the tumors of epidermoid type, that of a 59 year old man, developed in a scar following operative treatment for equino-

varus at the age of 14. The scar had never healed satisfactorily but had given rise to superficial ulcerations. The remaining 2 epidermoid tumors developed, one in a varicose ulcer of twenty-five years' duration and the other in an ulceration following milk leg twenty-three years previously.

HANDS

Table 1c shows that the hands were the site of epidermoid carcinoma in numerous cases (152 cases in the Massachusetts Diagnostic Service) and of basal cell carcinoma in a few (26 cases). Only 2.1 and 1.4 per cent of all the basal cell, but 17.8 and 16.2 per cent of all the epidermoid tumors occurred on the hands. Of the neoplasms of this site, only 15 and 11 per cent were basal cell carcinoma. The hands, then, have a decided predilection for epidermoid carcinoma.

Tumors of the hands developed most frequently in males (69 and 75 per cent).

Table 1c also shows that nearly all of the tumors (28 of 36, or 78 per cent) were observed on the dorsa of the hands. Only a few tumors developed on the palms and fingers.

One of the 36 tumors of this group developed from a preexisting scar (table 2). This occurred on a finger of a male patient at the site of a severe burn that occurred two years prior to the onset of the tumor. It was diagnosed as basal cell carcinoma.

The percentage of epidermoid tumors metastasizing from the hands was 16.

FEET

Only in 10 cases in the series of the Massachusetts Diagnostic Service was carcinoma observed in the skin of the feet (table 1c). The tumors in this group comprised about 0.5 per cent of all the cutaneous tumors. Only 1 was basal cell in type. The feet, like the hands, appear to have a decided predilection for epidermoid carcinoma. Six of the 10 tumors occurred in males.

A COMPARISON OF TUMORS OF DIFFERENT SITES

Incidence.—It can be seen from tables 1a, 1b and 1c that the sites differed in frequency of development of cutaneous carcinoma. The different frequencies are represented graphically in chart 1, which was constructed from the data of the Massachusetts Diagnostic Service. The chart shows that of the 856 tumors diagnosed as epidermoid carcinoma, 24.4 per cent occurred on ears, 17.8 per cent on hands and 16.8 per cent on the upper parts of faces. Evidently the sites most commonly affected by this type of neoplasm were the ears, the hands and the upper part of the face. In contrast, the nose, lower part of the face, trunk and neck were less frequently affected (the nose in 10.3 per cent of the cases and

the neck in 6.3 per cent). The scalp, arms, legs and feet were only occasionally affected (the scalp in 2.5 per cent of the cases and the feet in 1.1 per cent).

The basal cell carcinoma localized most frequently on the upper part of the face (30.0 per cent), nose (18.8 per cent), ears (15.6 per cent) and lower part of the face (13.9 per cent). The trunk and neck were less commonly affected (7.2 and 6.2 per cent, respectively). The scalp, arms, legs, hands and feet were only infrequently the sites of this type of cutaneous tumor (the scalp in 2.9 of the cases and the feet in 0.1 per cent).

It is evident from chart 1 that the two groups of tumors differed in their localization. The sites of predilection for epidermoid carcinoma

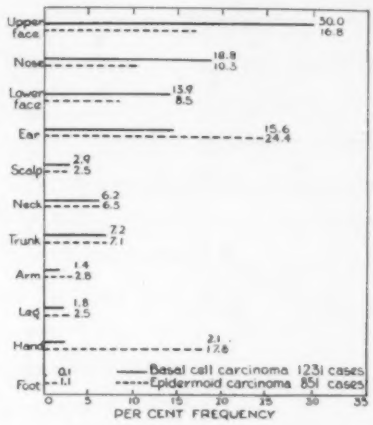

Chart 1.—The relative incidence of cutaneous carcinoma in various sites.

were, in order of frequency, the ears, the hands and the upper part of the face, while for basal cell carcinoma the common sites were the upper part of the face, the nose and the ears.

Another method of studying the relationship between site and type of tumor is given in chart 2. This chart, based on data of the Massachusetts Diagnostic Service, shows the percentage of tumors diagnosed as basal cell carcinoma for each site. It is seen that 69 per cent (in males) and 76 per cent (in females) of the tumors of the upper part of the face and of the nose were basal cell carcinoma. Similarly a high percentage of the tumors of the lower part of the face were basal cell carcinoma (66 per cent in males, 77 per cent in females).

Tumors of the neck, trunk and scalp were relatively infrequent, but of those that did occur, a majority (54 to 68 per cent) were basal cell carcinoma.

In contrast, 25 per cent or less of the tumors of the hands and feet were basal cell and more than 75 per cent were epidermoid. Of those on the arms and legs, 39 to 52 per cent were basal cell. Of the tumors of the ears, 42 per cent in the males and 70 per cent in the females were basal cell.

In brief, carcinoma in any site of the skin except the male ear or an extremity was more likely to be basal cell than epidermoid in type. A tumor on a hand or a foot was very likely (8: 10) to be epidermoid carcinoma.

Sex.—The effect of sex on the occurrence of the two types of tumors was studied in tables 1a, 1b and 1c by determining the percentages of

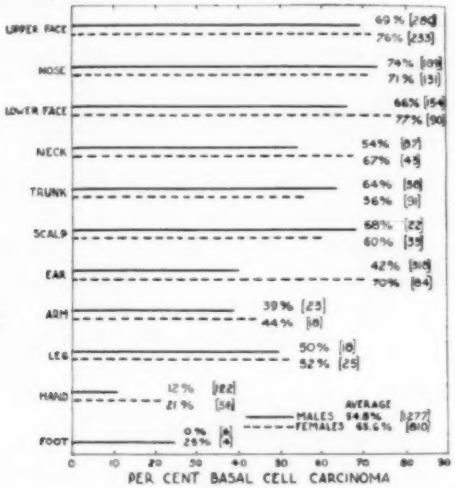

Chart 2.—The percentage of basal cell carcinoma according to site.

males with a particular type of carcinoma. Fifty per cent represents, of course, equal numbers of male and female patients. A percentage greater than 50 indicates male preponderance and a percentage less than 50 female preponderance. The percentage of males with a given type of carcinoma is given for each site in chart 3 (constructed from data of the Massachusetts Diagnostic Service).

The chart shows that the percentage of males for the basal cell carcinoma group varied with site from 41 to 69, with an average of 57. Of the tumors at most sites, more developed in males than in females. The greatest male preponderance was observed in reference to tumors of the ears (69 per cent males, or 2.3 males to 1 female). The three sites which had a female preponderance were the scalp, the trunk and the legs (42, 42 and 41 per cent males).

The percentage of males for the epidermoid carcinoma group varied with site from 34 to 88, with 67 per cent for all sites. These neoplasms

were associated, then, with a more marked male preponderance than the basal cell tumors. The male preponderance was observed for nearly all sites and was particularly high for epidermoid tumors of the ears (88 per cent males, or 7.3 males to 1 female). The percentage of males was also high for tumors of the neck (74) and the lower part of the face (71).

The three sites that showed female preponderance for epidermoid carcinoma were the scalp, the trunk and the legs (33, 34 and 43 per cent males). It will be noted that the same sites also showed female preponderance for basal cell tumors.

Preexisting Scars.—Table 2 gives a comprehensive summary of the number and location of tumors that developed in preexisting scars for cases of Pondville Hospital. The table shows that 2.8 per cent of all

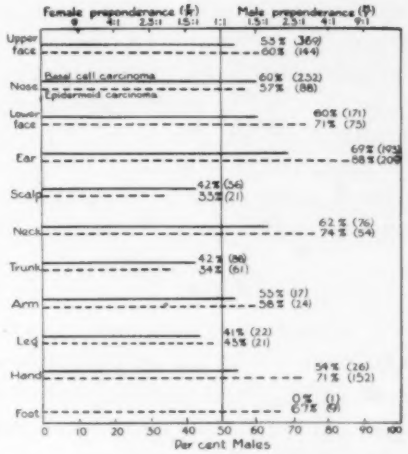

Chart 3.—A graphic representation of the relative numbers of males and females in whom cutaneous carcinoma develops at each site.

the tumors occurred in scars. However, the percentage of "scar tumors" was quite high in certain sites: the leg (44 per cent), the scalp (17 per cent), the arm (13 per cent) and the trunk (9 per cent). Of 60 tumors in these four sites, 11 or 18 per cent, developed in scars. In contrast, of the 433 tumors of other sites, only 3, or 0.7 per cent, occurred in scars. The differences in the percentages are found, by use of a nomogram,[3] to be statistically significant.

These "scar tumors" are known definitely to have developed in scars. The question remains, however, whether carcinoma is more prone to develop in the altered epithelium of scarred tissue than in normal tissue. This cannot be answered directly since it is not possible

3. Schrek, R.: J. Lab. & Clin. Med. **25**:180, 1939.

to determine the percentage of scars that became malignant. It has been shown, however, that 18 per cent of the tumors of the scalp, trunk, arms and legs developed in scars. This high percentage indicates strongly that the scar tissue itself or the previous injury was an important factor in the origin of the carcinoma.

The scars resulted from such traumas as extensive burns, roentgen ray burns, lacerations and surgical operations. These injuries took place as long as forty years prior to the onset of carcinoma. In some of these cases it seems that a single traumatic injury was followed by the development of carcinoma. This does not mean that the injury itself caused the tumor, but apparently the scarred skin was more susceptible to the development of carcinoma than normal skin.

Metastasis.—Table 3 shows that in 16 per cent of all cases of cutaneous epidermoid carcinoma the growth metastasized to regional lymph nodes. The percentages of metastasis for the different sites varied from 0 to 30, but the differences in the percentages are not statistically significant. It is to be observed in table 3 that those sites with large series of tumors had approximately the same percentage of metastasis (20 per cent for the upper part of the face, 14 per cent for the ears and 16 per cent for the hands). It may be concluded that site has no appreciable effect on the percentage of metastasis of cutaneous epidermoid carcinoma.

SUMMARY

This paper presents an analysis of the data on two types of cutaneous carcinoma with special reference to the various regions of the skin.

Epidermoid carcinoma has a marked predisposition for the ears, the hands and the upper part of the face, in order of frequency; whereas basal cell carcinoma prefers the upper part of the face, the nose and the ears.

Both types of carcinoma occurred with higher frequency in males than in females. This male preponderance was especially marked for tumors of the ears. On the other hand, the neoplasms of the scalp, trunk and legs were somewhat more frequent in females.

A fairly high proportion (18 per cent) of the tumors of the scalp, trunk, legs and arms developed in preexisting scars, which were produced by such injuries as burns, lacerations, surgical operations and ulcerations. It is believed that the scarred skin is more susceptible to the development of cutaneous carcinoma than normal skin. If this is so, it follows that a single traumatic injury may ultimately result in carcinoma.

About 16 per cent of the cutaneous tumors diagnosed as epidermoid carcinoma metastasized to regional lymph nodes. As far as could be determined, the site of the tumor did not affect appreciably the percentage of metastasis.

MEDIAL CORONARY SCLEROSIS IN INFANCY

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Perhaps the most interesting, and not the least important, type of coronary disease occurring in infancy is that which develops as a part of the process of general medial calcification of the arteries. Six cases, reports of which have been abstracted from the literature, and 1 case of our own are important clinically because of ischemic phenomena apparent in the myocardium, with which the coronary lesions were associated, as judged by clinical signs in some cases and by histologic sections in others. The accompanying table presents a résumé of these findings with the addition of other data of interest. It does not include cases of arterial calcification in infants in which the coronary arteries were not mentioned,[1] nor cases of visceral calcifications in infants in which the general arterial system was uninvolved [2] or not mentioned.[3]

The arterial changes occurring in the first 6 cases noted in the table are essentially the same as those in the case which we report except that in some the calcifications involved the aorta and its major branches in addition to the coronary arteries.

REPORT OF A CASE

A boy was born of a healthy primiparous 21 year old mother. The mother's Kahn test was negative. The father appeared healthy. The mother had received approximately 850 units of vitamin D and 4,700 units of vitamin A (U. S. P.) in a concentrate oil daily for ten weeks in the latter half of her pregnancy. The child was born, July 24, 1937, by a spontaneous left occipital-anterior delivery after seventeen hours of labor. It weighed 6 pounds 4 ounces (2,835 Gm.) and measured 49 cm. in length at birth. The eyes reacted to light, the heart sounds were good, the chest was clear, and there was no nasal discharge. The boy was breast fed until October 29, one week before his death. Then he began to receive 5 drops of what is believed to have been cod liver oil concentrate daily (500 U. S. P. units of vitamin D and 4,800 U. S. P. units of vitamin A) with his formula of cow's milk. He developed normally and gained weight. On being

From the departments of pathology and pediatrics of the St. Francis Hospital.

1. Durante, G.: Bull. et mém. Soc. anat. de Paris **74**:97, 1899. Johansson, S.: Acta radiol. **1**:17, 1921-1922. Jaffé, R.: Frankfurt. Ztschr. f. Path. **15**:118, 1914. Köhler: Fortschr. a. d. Geb. d. Röntgenstrahlen **31**:52, 1923; cited by Thomasen.[16]

2. Thatcher, L.: Lancet **1**:20, 1936.

3. Marsden, J. P.: Brit. J. Child. Dis. **27**:193, 1930.

questioned, the mother recalled that he seemed less active than other babies and frequently did not sleep well the first part of the night. On the night before death, November 5 (aged 3½ months), he suddenly became dyspneic and cyanotic, and vomited once. When admitted to the hospital the following morning he appeared to be dying. He was alternately pale and cyanotic, the respirations were very rapid, and the heart sounds were too rapid to count. Epinephrine and codeine appeared to give slight relief, but after two short tonic convulsions the child died, less than

Summary of Data on Seven Cases of Medial Coronary Sclerosis in Infants

Author *	Date	Age and Sex	Coronary Arteries †	Cardiac Signs	Kidneys	Parathyroids	Other Data
Bryant and White [22]	1901	6 mo.; male	Calcified, hard and narrow	None; terminal gangrene of foot	Congenital urethral dilatation	Not mentioned	No viosterol; visceral calcifications noted
Surbek [21]	1917	3 days; male	Calcified but not occluded	Sudden death as from heart failure	Focal glomerulonephritis; fibrinous pericarditis	Not mentioned	No viosterol; no bone change; visceral calcifications
Hughes and Perry [23]	1929	7 wk.; female	Calcified and lumen obliterated	Sudden cyanosis and death	Not mentioned	Not mentioned	No viosterol; no visceral calcifications
Forrer [20]	1930	3 mo.; male	Calcified with intimal thickening	Fatty myocardial change	Low grade glomerulonephritis	Not mentioned	No viosterol; no visceral calcifications
Iff ‡	1931	1 day, 8 mo.; premature male	Calcified with intimal fibrosis	Ascites and subcutaneous edema	Glomerular and intertubular foci of calcification; no renal infection	Not abnormal	No viosterol; no bone change; visceral calcifications
Lightwood [24]	1932	2 yr., 3 mo.; female	Calcified with intimal proliferation	Sudden death; focal myocardial degeneration, probably from coronary occlusion	Glomerular fibrosis; glomerular and tubular calcification	Not enlarged; serum calcium 11 mg. %; phosphorus 6.6 mg. %	Scott's emulsion; lime water; bone changes; visceral calcifications
Brown and Richter	1940	3 mo.; male	Calcified; lumen obliterated	Cyanosis and sudden death; focal myocardial necrosis	No significant change	Not described	Viosterol given; no visceral calcifications

* No attempt has been made to review cases from the literature prior to 1930, when Zeek's review of juvenile arteriosclerosis appeared (Arch. Path. **10**: 417, 1930).

† Other arteries besides the coronary vessels were involved in all cases.

‡ Ausgedehnte Gefassverkalkung im frühen Kindesalter, Inaug. Dissert., Zurich, 1930; cited by Iff.[19]

twenty-four hours after the onset of the symptoms. Blood taken before death showed hemoglobin 80 per cent, white cells 13,700, neutrophils 40 per cent and lymphocytes 60 per cent. The rectal temperature was 99 F. The clinical impression was: acute cardiac decompensation or an acute allergic reaction.

A postmortem examination was made two and one-half hours after death. The height was 59 cm. and the weight 13 pounds (5,896.5 Gm.). The external appearance was entirely normal. The peritoneum contained 100 cc. of clear fluid and each pleural cavity 200 cc. of thin blood-tinged fluid. The pericardium was normal. The heart weighed 48 Gm. (average normal, 27 Gm.); the tricuspid valve measured 4.5 cm., the pulmonary valve 2.3 cm., the mitral valve 4.5 cm. and the aortic valve 2.5 cm. The right ventricle measured 0.3 cm. in thickness, the left

0.7 cm. The heart, particularly the right ventricle, appeared slightly enlarged. The epicardium was smooth, the myocardium was pale, and the endocardium displayed superficial smooth white streaks. On the line of closure of the mitral and tricuspid leaflets were occasional minute smooth blood-stained elevations. The coronary arteries appeared more prominent and tortuous than usual but were not sufficiently abnormal to excite suspicion. Unfortunately, the parathyroids were not examined, and sections of the skeleton were not cut. The ribs, vertebrae and extremities, however, were noted to be normal in the gross examination; likewise, the aorta, vena cava, lungs (60 Gm. each), gastrointestinal tract, liver (200 Gm.), gallbladder, spleen (14 Gm.), kidneys (28 Gm. together), ureters, bladder, pancreas and adrenals.

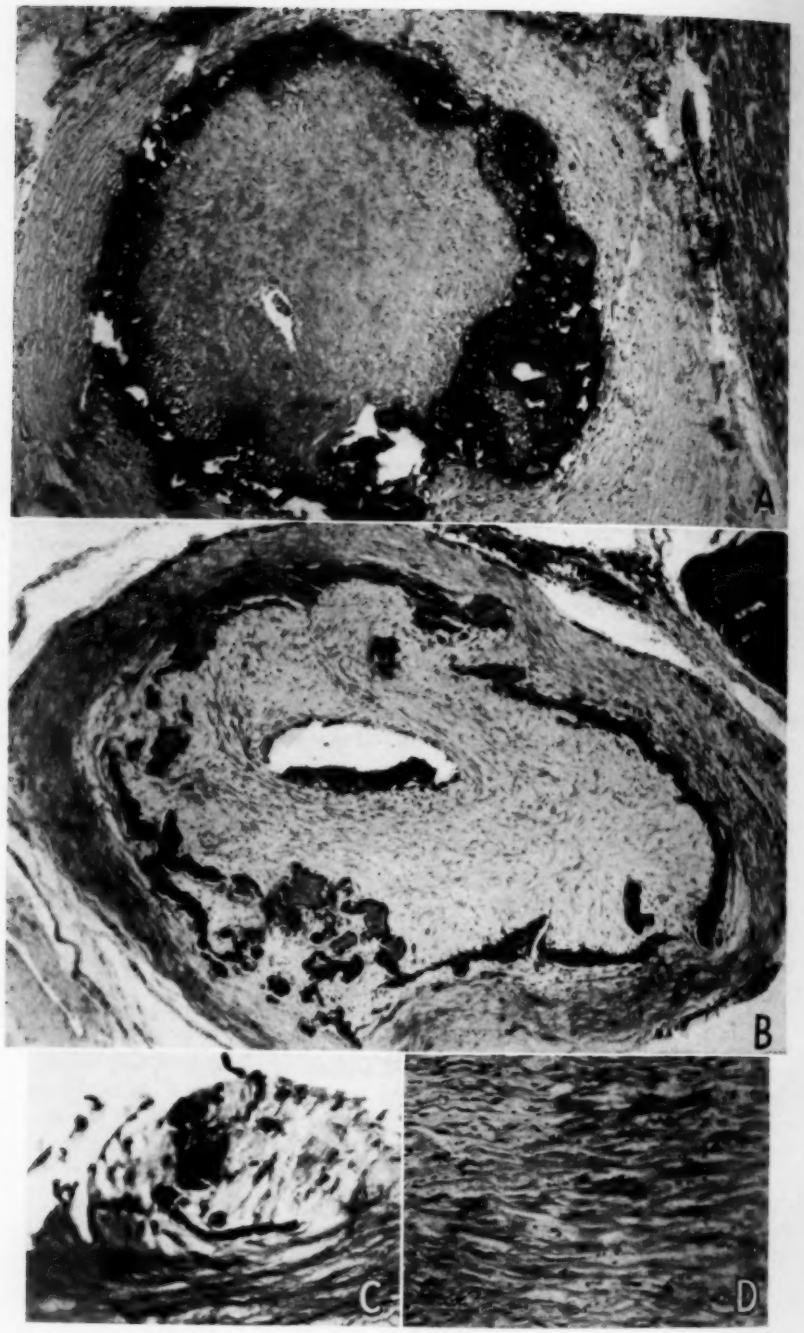
The mesenteric lymph nodes measured 1 cm. in diameter and were soft and gray.

The arteries of the extremities were not examined.

Microscopic Examination.—Heart: Both the coronary arteries and their major branches were involved in extensive changes, characterized by disruption and calcification of the internal elastica, edema and fibroblastic proliferation of the intima, and atrophy of the muscle fibers of the media. The changes were furthest advanced in the circumflex branch, where the lumen was almost totally obliterated by a random scattering of numerous fibroblasts in a pale, pink intercellular amorphous substance resembling hyalin. The media was completely replaced with masses of intensely basophilic material containing crystal fragments resembling calcium or calcium salts (*A* in the figure). The adventitia exhibited collagenous thickening, this finding being shared only by the small intramyocardial branches of the coronary arteries. The process in another portion of the left circumflex and in the right coronary artery was nearly as far advanced. Here the proliferating intimal fibroblasts lay in a loose, edematous matrix. Scarlet red stains for lipoids gave negative results. The calcification of the internal elastica was marked, but the membrane still retained its acidophilic properties and could be identified easily in places as a thin line within the calcium strands (figure, *B*). Scattered smooth muscle fibers were discernible in the outer layers of the media. An earlier stage was seen in a section of the left anterior descending branch. Here the internal elastica could again be identified as an irregularly thickened band, on which calcium appeared encrusted. Wandering cell infiltrations were at a minimum. In *C* in the figure the earliest stages of the process are seen.

Here the elastica stain brings out the beading and atrophy of the internal elastica and the overlying intimal proliferation and edema. In addition, opaque amorphous foci are seen in the intima, which with hematoxylin and eosin take a pinkish purple hue resembling the fibrinoid lesions discussed by Clark, Graef and Chasis.[4] These foci did not take the deep blue basophilic stain characteristic of calcium, but the purplish tint at their edges suggests early deposition of this material. Sections were taken in all regions of the heart according to the method of Gross and co-workers. The lesions on the mitral and tricuspid valves were made up of ectatic capillaries. The endocardium, particularly in the auricles, was thickened. In the section through the left ventricle and posterior papillary muscle numerous myocardial fibers appeared opaque, finely granular and disrupted. Hemorrhages and neutrophilic infiltrations associated with these changes (*D* in the figure) suggest infarction, although foci of myocardial necrosis from which this lesion cannot be distinguished, have been demonstrated in rats poisoned with

4. Clark, E.; Graef, I., and Chasis, H.: Arch. Path. **22**:183, 1936.



(See legend on opposite page)

vigantol (a preparation of irradiated ergosterol). A von Kossa stain of this focus showed no calcification, while sections of the coronary arteries were deeply blackened in the zones of calcification.

Aorta: Sections through the arch showed no changes.

Kidney: In most of the glomeruli the cells of the capillary loops were swollen and the lumens relatively scanty. The epithelium of the convoluted tubules was swollen. The remainder of the tubules and arterioles appeared normal. An arcuate artery seen in longitudinal section displayed calcification of its internal elastica and media for about a fifth of its extent. The elastica in the involved portion was irregularly thickened, and the muscle fibers of the media were opaque and blue. Here no intimal proliferation was apparent.

Adrenal: A small artery in the pericapsular fat was involved in the same changes noted in the arcuate artery of the kidney.

Lung: The alveolar spaces were partially obliterated by apparent collapse of their walls.

Spleen, Liver, Thymus: These organs were normal.

COMMENT

The vascular calcifications described are essentially similar to those occurring in patients with renal insufficiency due to alterations in the blood calcium and phosphorus [5] or tumor of the parathyroids [6] or extensive primary bone disease [7] and in experimental animals following overdosage with parathyroid extract [8] or vitamin D [9] or following subcutaneous, intravenous or intraperitoneal injections of calcium salts.[10] It is apparent that the conditions named entail a systemic disturbance with alterations in the blood calcium and phosphorus. Furthermore, it has been presumed on good experimental grounds that this systemic distur-

5. Smyth, F. S., and Goldman, L.: Am. J. Dis. Child. **48**:596, 1934. Castleman, B., and Mallory, T. B.: Am. J. Path. **13**:553, 1937.

6. Dawson, J. W., and Struthers, J. W.: Edinburgh M. J. **30**:421, 1923.

7. Wells, H. G.: Arch. Int. Med. **15**:574, 1915.

8. Hueper, W.: Arch. Path. **3**:14, 1927.

9. Herzenberg, H.: Beitr. z. path. Anat. u. z. allg. Path. **82**:27, 1929. Shohl, A. T.; Goldblatt, H., and Brown, H. B.: J. Clin. Investigation **8**:505, 1930.

10. Tanaka, M.: Biochem. Ztschr. **35**:113, 1911; **38**:285, 1912. Katase, A.: Beitr. z. path. Anat. u. z. allg. Path. **57**:516, 1914.

Explanation of Figure

A, left circumflex coronary artery. Hematoxylin and eosin; low power magnification.

B, right coronary artery. Hematoxylin and eosin; low power magnification.

C, early change in the intima of a coronary artery. Verhoeff's elastica stain; high power magnification.

D, focus of necrosis in the posterior papillary muscle of the left ventricle. Hematoxylin and eosin; high power magnification.

bance is sufficient for metastatic calcifications in tissue not the site of previous degenerative changes.[11]

In some of the clinical group under discussion, alterations in blood calcium and phosphorus may be inferred from the coexistent renal damage, while in others the severity of the renal change is not sufficient to justify this. Minor to severe degrees were noted in most cases (table). Evidence of advanced inflammatory or obstructive damage is strong in the cases of Bryant and White and of Lightwood, and fairly good in those of Forrer and Surbek. In the latter cases it is possible that the glomerular changes were secondary to calcium deposition from a primary cause elsewhere, and in Iff's case this is highly probable. The swelling of the glomerular epithelium in our patient cannot be considered sufficient to invoke profound calcium-phosphorus alterations. Judging from similar arterial and visceral calcifications noted in older age groups in which alterations of blood calcium and phosphorus levels were observed that were known to result from renal insufficiency, it is fair to assume that renal insufficiency may have been of primary importance in about half of these infants.

Incomplete study of the blood and insufficient anatomic data, as well as certain forthcoming features of the clinical history, have inclined some authors to ascribe importance to other etiologic possibilities. The presence of a focus of infection at the time of death in Forrer's case caused him to attribute the arterial changes to a primary arterial degeneration from infection with an unknown agent. Lightwood emphasized no cause for the arterial changes in his case but was sure that they were not due to administration of vitamin D. Bryant and White expressed the belief that the lesions in their case resulted from "something more than a mere primary calcification" and assigned significance to some intrauterine influence on account of the severity of the lesions compared with the short time for their development. Hughes and Perry also decided that the calcification was of such a degree that it must have occurred during intrauterine life. There is no doubt that the arterial calcifications in Iff's 1 day old premature infant were acquired in utero. This author insisted that primary arterial damage preceded the calcific changes. The normalcy of the bones and parathyroids and the absence of extensive renal damage lend support to his contention that an incomplete maturation of the ground substance may have been of primary importance. However, the ectopic foci of calcification in the thyroid, kidney, placenta and elsewhere suggest a humoral influence. No history of viosterol intake on the part of the mother was reported. Surbek concluded that the ectopic calcifications in his 3 day old infant must have been due to "calcium gout" secondary to chronic nephritis developing as

11. Ham, A. W., and Lewis, M. D.: Arch. Path. **17**:356, 1934.

a result of an intrauterine infection. In the absence of inflammatory or obstructive renal changes or of gross osseous abnormalities in our case we can mention only the possibility of primary hyperparathyroidism, alteration of the calcium-phosphorus balance from the administration of viosterol to the mother and the child or some innate degenerative arterial change in the child.

Our data on the use of viosterol is not sufficiently complete, nor is the literature on the administration of moderate doses of vitamin D to the mother or the child sufficiently conclusive, to exclude this possibility, but it is highly unlikely. From the work of Vanderveer [12] and that of Ham and Lewis [11] has evolved the fact that by giving rabbits and rats massive doses of viosterol one can produce medial calcification and intimal proliferation in the walls of the arteries, lesions which appear essentially similar to those in the clinical cases under discussion. Cowdry and Scott [13] showed that intimal thickening of a mild degree occurred in the elastic arteries of rhesus monkeys given doses of vitamin D considered by them to be small but computed by Reed and co-workers [14] to be well above the toxic level for man. Arterial calcifications alleged to have resulted from viosterol overdosage and verified roentgenologically have been reported by Eisler [15] and by Thomsen.[16] Thatcher [2] reported the death of an 11½ month old boy who received a teaspoonful of cod liver oil three times daily over a period not exactly known. The kidneys and walls of the great arteries contained innumerable deposits of calcium, a change he considered pathognomonic for hypervitaminosis D. The recent monograph by Reed, Struck and Steck,[14] on the other hand, is replete with references to instances of massive doses of viosterol being given both to children and to adults with no resulting harm so far as could be judged clinically. Shelling and Hooper,[17] in tissue examinations of 27 children who received moderate doses of vitamin D for varying periods, could find no changes attributable to its use. In addition, no effects ascribable to overdosage were noted in several hundred children treated with viosterol in sometimes ten to twelve times the prophylactic dose for rickets. The amount of vitamin D given to the infant reported by Lightwood and to ours is in no sense comparable to the doses given experimentally to produce similar lesions in animals.

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12. Vanderveer, H. L.: Arch. Path. **12**:941, 1931.

13. Cowdry, E. V., and Scott, G. H.: Arch. Path. **22**:1, 1936.

14. Reed, C. I.; Struck, H. C., and Steck, I. E.: Vitamin D: Chemistry, Physiology, Pharmacology; Experimental and Clinical Investigation, Chicago, University of Chicago Press, 1939.

15. Eisler, F.: Klin. Wchnschr. **92**:1846, 1930.

16. Thomasen, E.: Acta med. Scandinav. **93**:505, 1937.

17. Shelling, D. H., and Hooper, K. B.: Bull. Johns Hopkins Hosp. **58**:137, 1936.

The obvious occurrence of vascular calcifications during intrauterine life in Iff's and Surbek's cases introduces the necessity of mentioning the meager data on possibly contributory maternal factors. The arterial changes in our case as well as in those in which the changes became apparent a few months after birth probably had their origin in intrauterine life also, but the extreme rapidity with which rats display arterial calcifications after viosterol poisoning does not allow us to assume a congenital origin for them. Brehm [18] published some interesting data concerning the effect of moderately high doses of viosterol given the mother on the fetus and placenta. He conducted an investigation in a series of 540 obstetric patients, one sixth of whom received from early pregnancy 5 drops of viosterol three times daily for two weeks alternately with 5 grains (0.32 Gm.) of calcium three times daily for two weeks. Another sixth of the series received viosterol alone, while the remaining groups received calcium and cod liver oil alone and jointly, and one received nothing. From the data one assumes that in the first two groups the incidence of calcification of the placenta and of premature closure of the fontanels was well above that in the remaining groups. In the first group 3 stillborn infants had calcification of the kidneys.

Iff [19] made no mention of the maternal use of vitamin D in his own report of a case or in his review of Forrer's [20] case. The infants described by Surbek [21] and by Bryant and White [22] were born before the advent of vitamin D concentrates. Vitamins were not mentioned by Hughes and Perry [23] in their description of a case. The survival of the infant described by Lightwood [24] for over two years after birth does not favor the theory that the acquisition of the arterial lesions is congenital. From this group of cases we can see no suggestion of a relationship between maternal use of vitamin D concentrates and arterial calcifications in infants. In our case the moderate amount of viosterol received by the mother certainly appears insufficient to produce any degree of hypercalcemia.

Another situation in which significant alterations in maternal levels of calcium and phosphorus occur is that of hyperparathyroidism. It is fair to assume in regard to cases 4 and 20 of the Castleman and Mallory [25] series that the mothers experienced hyperparathyroidism during

18. Brehm, W.: Ohio State M. J. **33**:990, 1937.

19. Iff, W.: Virchows Arch. f. path. Anat. **281**:377, 1931.

20. Forrer, H.: Ausgedehnte Gefässverkalkung im frühen Kindesalter, Inaug. Dissert., Zurich, 1930; cited by Iff.[19]

21. Surbek, K.: Centralbl. f. allg. Path. u. path. Anat. **28**:25, 1917.

22. Bryant, J. H., and White, W. H.: Guy's Hosp. Rep. **40**:17, 1891.

23. Hughes, F. W. T., and Perry, C. B.: Bristol Med.-Chir. J. **46**:219, 1929.

24. Lightwood, R.: Arch. Dis. Childhood **7**:193, 1932.

25. Castleman, B., and Mallory, T. B.: Am. J. Path. **11**:1, 1935.

pregnancy and that the elevated blood calcium noted subsequently was probably present during pregnancy. The child of one of the patients was noted to be normal at birth, and the health of the other infant was not mentioned. The failure of these infants to exhibit metastatic calcifications in spite of the almost certain maternal hypercalcemia suggests that this assumed hypercalcemia either had no effect or had at most a subclinical effect on the state of the fetal tissues.

Coincident infection of the infant, noted only in the cases of Forrer (navel infection) and Surbek (pericarditis), offers insufficient grounds for acceptance of the infection theory, and the various other arterial noxious agents, such as epinephrine, may be discarded similarly for lack of supportive data. The tendency for elastica tissue to undergo calcification is well known. Minor alterations in the composition or colloidal state of this type of ground substance undoubtedly occur without giving rise to tinctorial changes, or more pronounced changes may be observed as evident in C in the figure. It is probable that either changes in the composition of the vascular elastica or minor elevations of the blood phosphorus or calcium in an organism in which deposition of calcium is occurring at a high rate will result in calcification at favorable sites. Such changes also appear to account for the associated intimal proliferations. That these calcifications and intimal proliferations involving the coronary arteries exert ischemic effects on the myocardium is evident either from the type of death or from the myocardial lesions observed in most infants in the group.

SUMMARY

A case of coronary calcification in infancy is reported with data on 6 additional cases abstracted from the literature. This type of vascular change is a part of general arterial calcification, the chief site of which appears to be the internal elastica. Coexistent intimal proliferations are noted frequently. These may result at times in occlusion. The cause of the lesion is in doubt, although some alteration in the calcium and phosphorus metabolism is suspected.[26]

26. S. W. Lippincott has recently reported (Am. J. Path. **16**:665, 1940) calcifications of the small arteries and dystrophic calcifications in the heart, kidney, lung and stomach of a 10 month old infant who received forty to sixty-five times the proper dose of vitamin D daily for eight months.

RELATION OF THE CONCENTRATION OF RED BLOOD CELLS TO THE SENSITIVITY OF THE ISOAGGLUTINATION REACTION

ITS IMPORTANCE IN THE DEMONSTRATION OF AGGLUTININ IN DRIED BLOOD STAINS

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The various tests which are based on the phenomenon of isoagglutination are of sufficient importance both in clinical and in forensic medicine that advantage should be taken of every possibility by which their sensitivity or accuracy may be improved.

There is special need for refinement of the methods employed in determining the group of the dried blood stain. The methods commonly used are inadequate to such a degree that in only a small proportion of cases in which grouping of dried stains is undertaken are informative results obtained (Lewinski [1]).

The group of a dried stain may be determined by demonstrating the specific isoagglutinins or isoagglutinogens contained in the stain. According to most observers, the demonstration of agglutinins in dried stains is difficult or impossible in the vast majority of cases. The demonstration of agglutinogens by the absorption technic has become the method of choice, and although this method has been proved to be sensitive and specific (Boyd and Boyd;[2] Landé [3]), it has definite limitations in actual practice. The interference with the absorption test by nonspecific absorptive agents or by contaminating foreign agglutinogens (Therkelsen;[4] Hirszfeld and Amzel;[5] Hirszfeld;[6] Lewinski [1]), together with the fact that a negative result is inconclusive, are among the more important factors which curtail the usefulness of this test. A negative result may be due to a technical failure rather than to actual absence of agglutinogen. A_2 agglutinogens are especially likely to be

From the Department of Legal Medicine, Harvard Medical School.

1. Lewinski, W.: Deutsche Ztschr. f. d. ges. gerichtl. Med. **27**:194, 1937.
2. Boyd, W. C., and Boyd, L. G.: J. Immunol. **33**:159, 1937.
3. Landé, K. E.: Arch. Path. **25**:463, 1938.
4. Therkelsen, F.: Ztschr. f. Rassenphysiol. **8**:98, 1936; **9**:1, 1937.
5. Hirszfeld, L., and Amzel, R.: Deutsche Ztschr. f. d. ges. gerichtl. Med. **19**: 132, 1932.
6. Hirszfeld, L.: Deutsche Ztschr. f. d. ges. gerichtl. Med. **27**:189, 1937.

overlooked (Therkelsen;[4] Boyd and Boyd[2]). Moreover, the absorption test offers no positive proof with respect to group O, to which the blood of 40 per cent or more of the population belongs.

The percentage of satisfactory results in the grouping of dried stains would be materially increased if the agglutinin in dried blood could be consistently demonstrated. In human blood there is a reciprocal relationship of agglutinin and agglutinogen—where one is absent, the other is present. Thus a negative result of the absorption test would be confirmed if the corresponding agglutinin were demonstrated, and the sum of the results of both tests would be positive proof with respect to any major blood group, including group O.

Unfortunately, the present methods of producing isoagglutination are usually insufficiently sensitive to detect small traces of agglutinin. Even when there is ample dry blood stain to work with, the results in a great majority of cases are unsatisfactory (Holzer;[7] Therkelsen;[4] Hirszfeld and Amzel[5]).

In has long been known that variations in the concentration of antigen, antibody or electrolytes have significant quantitative and qualitative effects on antigen-antibody reactions (Marrack[8]). In attempting to demonstrate the presence of agglutinin in dried blood stains, it should be borne in mind that minimum quantities of antibody may be encountered. With this element fixed at a minimum, there remain two variable elements which must be altered in order to attain maximum sensitivity, namely, the concentration of electrolytes and the concentration of the erythrocytic suspension. This investigation concerns itself with the latter.

In most reference books, the recommended cell suspensions vary from 1 to 5 per cent in the initial dilutions, and the addition of an equal volume of serum, brings the final dilutions to between 0.5 and 2.5 per cent. Greater variations are mentioned in the literature. Hesser[9] calculated from the technics outlined by various investigators that the cell suspensions utilized varied from about 0.125 to 25.0 per cent final concentrations. He therefore examined the effectiveness of different concentrations of cell suspension, using as a criterion the degree of agglutination with a strong serum. He found that the optimum final cell concentration lay between 0.4 and 3 per cent. Whether or not Hesser's observation is valid for weak concentrations of antibody can be determined only by finding what concentrations of cells are most sensitive to high dilutions of serum.

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7. Holzer, F. J.: Deutsche Ztschr. f. d. ges. gerichtl. Med. **16**:445, 1931.

8. Marrack, J. R.: The Chemistry of Antigens and Antibodies, Medical Research Council, Special Report Series, no. 194, London, His Majesty's Stationery Office, 1934.

9. Hesser, S.: Acta med. Scandinav., 1924, supp. 9, p. 1.

It is generally known that heavy cell suspensions (10 per cent or more) are very insensitive and are obviously in the zone of antigen excess. Wiener [10] made the comment that "if an excess of cells is used, they may absorb all the agglutinins present in weak or diluted sera, but fail to agglutinate with such sera." However, he does not state the limits of this zone of antigen excess, and this is a most important consideration in regard to the detection of minimum quantities of agglutinin.

EXPERIMENTS 1 AND 2

Two experiments were undertaken with the thought that the concentrations of erythrocytes which are most sensitive to minimum amounts of agglutinin can be determined by making serum titer determinations with progressively decreasing concentrations of red cells.

In conducting such an investigation, two procedures may be followed: 1. The volume of antibody (dilute serum) may be kept constant and the amount of antigen (erythrocytes) may be varied. 2. The amount of antigen may be kept constant and the volume of antibody varied. For convenience of execution and for economy of materials, both procedures were utilized.

The first procedure was used in studying agglutination in cell suspensions which varied between 32 and 0.125 per cent final concentration. The final volume for all tubes in this group was kept at 0.2 cc. In the weaker suspensions of red cells (0.125 to 0.00048 per cent final concentrations) it was necessary to use the second procedure, increasing the total volume proportionately to the dilution of the cells. This preserved a constant number of erythrocytes, and after centrifugation a uniform quantity of red cell deposit was obtained.

The cells were mixed with progressive dilutions of serum and were uniformly dispersed by shaking or stirring. After centrifugation of the supensions (2,000 revolutions per minute for five minutes; radius, 19 cm.), the sediment was shaken until it was entirely released from the bottom of the test tube. The appearance of clumps was noted. If the reaction was negative or weakly positive, the cells were transferred to hanging drop preparations, allowed to stand a uniform length of time (at least thirty minutes), and the results were read microscopically.

In reading the reactions when extremely high dilutions of red cells were employed, centrifugation was an indispensable procedure. Otherwise the reaction was slow and the cells were so widely scattered that even if clumping occurred it was difficult to recognize either by gross or microscopic examination. Centrifugation caused aggregation of cells at the bottom of the tube, thereby hastening agglutination and making possible the formation of large clumps. The volume of supernatant fluid was secondarily reduced and readings were made by observing the presence of clumps when the sediment was resuspended.

In making microscopic readings of agglutination when large volumes of very dilute cells were used, the described procedures of centrifugation and removal of most of the supernatant fluid were necessary. These steps were adopted because it was found that a concentration of cells below 0.12 per cent did not afford satisfactory microscopic fields in hanging drop preparations. The cells were so sparse that positive results were not clearly defined. After centrifugation, most of

10. Wiener, A. S.: Blood Groups and Blood Transfusion, ed. 2, Springfield, Ill., Charles C. Thomas, Publisher, 1939.

the supernatant fluid was pipetted off, leaving about 0.2 cc. The precipitated cells were resuspended in this smaller volume, and thus a concentration of cells was obtained which was adequate for microscopic examination.

In experiment 1 the same serum (group B, Brown) and the same cells (group A, Lund) were used. The cells were always taken fresh (never over two hours old at the time of dilution and titration) and were washed three times with physiologic solution of sodium chloride. The concentration was determined by packing the cells at the bottom of a calibrated tube by centrifugation. The final dilution of erythrocytes, the final dilution of serum and the final volume in each tube are described in table 1. The results are expressed in plus and minus marks.

In experiment 2 group A serum (Monroe) was used against group B cells (Kingsley). The results are shown in table 2.

A composite of the results of experiments 1 and 2 is shown in the accompanying chart. Each mark indicates the highest dilution of serum in which a positive reaction was obtained with a given final concentration of erythrocytes. It will be noted that the 0.00048 per cent cell concentration of Oct. 16, 1940 (table 1) was not included in the composite graph. This was omitted because positive results were not obtained. Either the positive reactions occurred below 1 : 2,048 dilution or else there was a technical error. The scant grayish brown deposit obtained after centrifugation suggested that at least partial hemolysis took place.

EXPERIMENT 2 A

Experiments 1 and 2 reached the practical limits of volume increase. To go further would entail the use of unwieldy quantities. Experiment 2a was undertaken at a later date, to see whether or not the trend suggested in experiments 1 and 2 continues another two steps (to 0.00012 per cent final cell concentration). This involved the use of the maximum amount of fluid and a decrease of the antigen to one-fourth the standard amount used in the higher dilutions of the preceding experiments. After centrifugation, the total volume must be reduced markedly if a microscopic reading is desired (to about 0.05 cc.), and this small volume evaporates readily at the base of a large centrifuge tube. It was therefore necessary to centrifuge the original 50 cc. of suspension, reduce the supernatant to 0.5 cc., then transfer cells and fluid to a small tube (4 mm. inside diameter), centrifuge again and reduce the volume to 0.05 cc. Thus, the cells were recovered in the necessary small volume without danger of evaporation. A parallel test using 0.00195 per cent final concentration of cells was run. Its volume was reduced, the cells were resuspended, and it was centrifuged a second time to imitate the conditions of the 0.00012 per cent series. The results of this experiment are included in table 2.

COMMENT ON EXPERIMENTS 1, 2 AND 2 A

The three experiments indicate that the agglutinating titer of a given serum increases with progressive diminution of the relative quantity of the suspended red cells. The increase is inversely proportional to the concentration of cells except in the extremely high dilutions (0.0078 to 0.00012 per cent final cell concentrations), where there is a tendency to level off.

The results infer that the sensitivity of the reacting system depends on the amount of antibody available for each erythrocyte and this is

TABLE 1.—*Group B Serum vs. Group A Cells (Experiment 1)*

Date	Final Volume, Cc.	Final Concentration of Cell Suspension, per Cent	Final Concentration of Serum *												
			1:2	1:4	1:8	1:16	1:32	1:64	1:128	1:256	1:512	1:1,024	1:2,048	1:4,096	1:8,192	1:16,384
10/14/40	0.2	16.0	++	++	+	0	0	0								
	0.2	8.0	++	++	+	+	0	0	0							
	0.2	4.0	+++	++	++	+	+	+w	0	0						
	0.2	2.0	..	..	++	+	+	+	?	0						
	0.2	1.0	..	..	..	..	++	+	?	0	0	0				
	0.2	0.5	..	..	..	..	..	++	++	?	0	0				
	0.2	0.25	..	..	..	..	..	..	+++	+	+w	0	0			
	0.2	0.125	..	..	..	..	..	..	..	+++	+w	0	0			
	0.2	0.0625	..	..	..	..	..	..	..	+++	+++	+w	0			
10/15/40	0.2	0.125	..	..	..	..	..	..	..	+++	++	+w	0	0	0	0
	0.4	0.0625	..	..	..	..	..	..	..	+++	+++	+	0	0	0	0
	0.8	0.03125	..	..	..	..	..	..	..	+++	+++	++	0	0	0	0
	1.6	0.01562	..	..	..	..	..	..	..	+++	+++	+++	+	+	0	0
	3.2	0.00781	..	..	..	..	..	..	..	+++	+++	+++	+	+	?	0
	6.4	0.00390	..	..	..	..	..	..	..	+++	+++	+++	+++	++	?	0
10/16/40	0.2	32.0	..	+	+	+w	0									
	0.2	8.0	..	..	++	+	+w	0	0							
	0.2	1.0	..	..	..	..	..	++	+w	0	0	0				
	0.2	0.125	..	..	..	..	..	..	+++	++	+w	0	0	0		
	6.4	0.00390	..	..	..	..	..	..	..	..	..	+	+w	0	0	0
	50.0	0.00048	..	..	..	..	..	..	..	..	..	..	0	0	0	0
10/18/40	1.6	0.01562	..	..	..	..	..	..	..	+++	+++	+++	+	+	0	0
	3.2	0.00781	..	..	..	..	..	..	..	+++	+++	+++	++	+	0	0
	6.4	0.00390	..	..	..	..	..	..	..	+++	+++	++	+	+	0	0
	12.8	0.00195	..	..	..	..	..	..	..	+++	+++	+++	+++	+w	?	0
	25.6	0.00097	..	..	..	..	..	..	..	+++	+++	+++	+	+	0	0
	50.0	0.00048	..	..	..	..	..	..	..	+++	+++	+++	+++	+++	0	0

* +++ = very strong reaction—one or several large agglutinates and no haze; ++ = moderately strong reaction—fairly large agglutinates and slight to moderate haze; + = definite positive reaction—small agglutinates and haze (checked microscopically); +w = weak positive reaction (determined microscopically); ? = questionable reaction (determined microscopically); 0 = negative reaction (determined microscopically).

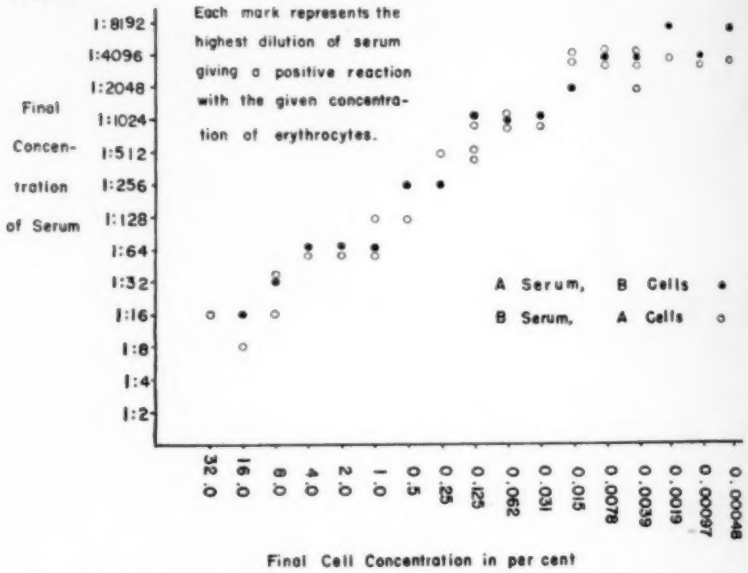
TABLE 2.—*Group A Serum vs. Group B Cells (Experiments 2 and 2a)*

Date	Final Volume, Cc.	Final Concentration of Cell Suspension, per Cent	Final Concentration of Serum *										
			1:8	1:16	1:32	1:64	1:128	1:256	1:512	1:1,024	1:2,048	1:4,096	1:8,192	1:16,384
10/22/40	0.2	16.0	+	+w	0	0								
Exper. 2	0.2	8.0	+	+	+	0	0							
	0.2	4.0	..	++	+	+w	0	0						
	0.2	2.0	..	..	++	+	0	0	0					
	0.2	1.0	..	..	..	+	0	0	0	0				
	0.2	0.5	..	..	..	..	++	+w	0	0	0			
	0.2	0.25	..	..	..	..	+++	+	?	0	0			
	0.2	0.125	..	..	..	..	..	+++	++	+w	0	0		
	0.4	0.0625	..	..	..	..	..	+++	++	+w	0	0	0	
	0.8	0.03125	..	..	..	..	..	..	..	++	?	0	0	0
	1.6	0.01562	..	..	..	..	..	..	..	+++	+	?	0	0
	3.2	0.00781	..	..	..	..	..	..	..	+++	+++	+	0	0
	6.4	0.00390	..	..	..	..	..	..	..	+++	+	+	?	0
	12.8	0.00195	..	..	..	..	..	..	..	+++	+++	+++	+	0
	25.6	0.00097	..	..	..	..	..	..	..	+++	+++	+	?	0
	50.0	0.00048	..	..	..	..	..	..	..	+++	+++	+++	+	0
10/31/40	12.8	0.00195	..	..	..	..	..	..	..	+++	+	+w	?	0
Exper. 2a	50.0	0.00012	..	..	..	..	..	..	..	+++	+	0	0	0

* For explanation of signs, see table 1.

determined not only by the concentration of antibody in a given serum but also by the relative volume of serum used in the reaction. This generalization agrees with the observations of Heidelberger and Kabat[11] on the quantitative chemistry of bacterial agglutination.

The fact that the increase of sensitivity did not continue at the expected rate in the extremely high dilutions but tended toward asymptote may have several causes. One of these is the increasing difficulty of bringing red cells into contact with every molecule of antibody as the relative volume of the reacting system is increased. The corrective effect of vigorous shaking or repeated centrifugation was not studied.



A graphic representation of the results of experiments 1 and 2, showing the serum titers determined by using progressively decreasing final concentrations of cell suspension.

The proportion of cells and serum to be used in the reaction of isoagglutination depends on the sensitivity desired. In ordinary hospital practice it is rarely necessary to attain maximum sensitivity and the lowest concentration of erythrocytes which maintains a satisfactory microscopic field should be used. It is well to keep in mind that the practical lower limits of cell concentration that can be used in a microscopic preparation are dependent on the thickness of the layer of suspension. Thus, a thin smear between a slide and cover slip, or a thinly smeared hanging drop, may require a 1 per cent cell suspension

11. Heidelberger, M., and Kabat, E. A.: J. Exper. Med. **65**:885, 1937.

to give a good field. On the other hand, an average hanging drop (about 0.01 cc., 5 mm. in diameter) retains a good field with as little as 0.125 per cent final cell concentration.

If maximum sensitivity is desired, extremely low concentrations of erythrocytes must be used and this entails the use of the centrifugal-reconcentration technic previously described.

EXPERIMENT 3

The practical value of using dilute cell suspensions for the identification of agglutinins in dried blood stains was next explored. A dry, powdered stain of

TABLE 3.—*Extract of Group O Blood Stain vs. Group B Cells (Experiment 3)* *

Final Concentration of Erythrocytes, per Cent	Final Concentration of Extract (Mg. Dry Stain per 0.1 Cc.)							
	16.0	8.0	4.0	2.0	1.0	0.5	0.25	0.125
1.0	+	+	0	0	0	0	0	0
0.25	++	+	+w	?	0	0	0	0
0.00625	++	++	++	+	?	0	0	0

Extract of Group O Stain vs. Group A Cells

Final Concentration of Erythrocytes, per Cent	Final Concentration of Extract (Mg. Dry Stain per 0.1 Cc.)						
	8.0	4.0	2.0	1.0	0.5	0.25	0.125
1.0	++	+w	0	0	0	0	0
0.25	++	++	+	0	0	0	0
0.00625	++	++	++	++	+w	?	0

* In each tube are 0.2 cc. of cell suspension and 0.2 cc. of extract. The dilutions given are final. For example, the final concentration of 8 mg. per 0.1 cc. together with a concentration of 1 per cent cells was attained by adding 0.2 cc. of 2 per cent cells to 0.2 cc. of an extract of 16 mg. per 0.1 cc. concentration. Note: In the first tube, a tenth volume of five times as strong a cell suspension was added in order not to dilute the strongest extract at hand (16 mg. per 0.1 cc.) to any significant degree and still attain the final dilution of cells listed. The tubes were centrifuged five minutes at 2,000 revolutions per minute. In the case of the 0.00625 per cent cell concentrations it was necessary to remove most of the supernatant fluid, leaving about 0.02 to 0.04 cc., in order to make the cell concentration sufficient for microscopic reading. The sediment was redispersed, and hanging drop preparations were made. Readings were made after thirty and sixty minutes.

All results are from microscopic readings: ++ = strong reaction—most of cells clumped; + = moderately strong reaction—a minority of cells clumped; +w = weak positive reaction—occasional small clumps; ? = questionable reaction; 0 = negative reaction.

group O, four and one-half months old, was weighed out and sufficient saline solution was added to make a concentration of 16 mg. of dried blood in each 0.1 cc. of solution. The extraction was allowed to progress two hours, and then the extract was centrifuged and the supernatant fluid transferred to another tube. To insure complete removal of debris, centrifugation was repeated. Progressive dilutions of the supernatant fluid were made. Three different final concentrations of erythrocytes (1, 0.25 and 0.00625 per cent, respectively) were tested to determine which could detect the smallest traces of agglutinin in the progressively diluted extract. Tests were made for the presence of both anti-A and anti-B agglutinin. The results are shown in table 3.

COMMENT ON EXPERIMENT 3

Using a strong reaction as the criterion, it is seen that the cell concentration of 0.00625 per cent was four times as sensitive as the

0.25 per cent series and eight times as sensitive as the 1 per cent series. This is a decided increase of sensitivity although not as great as would be expected from the results of the preceding experiments.

After the removal of the supernatant fluid from the cell sediment, it is possible to use the fluid again for agglutination with the opposite group of cells. This was tried experimentally with satisfactory, although slightly weaker, results.

A practical procedure for the detection of low concentrations of agglutinin in extracts of blood stains is indicated by the results of the foregoing experiments. A minimum dose of red cells and a maximum volume and concentration of extract are to be used. In practice the amount of extract usually is limited and the attainment of maximum sensitivity depends on the use of as few cells as possible, only sufficient to allow for the preparation of one or two hanging drops. If, after mixture of the cells with the extract, the final concentration of erythrocytes is less than 0.125 to 0.0625 per cent, which is the lowest concentration compatible with the preparation of a satisfactory microscopic field, it is necessary to regain this concentration by centrifugation and proportionate decrease of the volume of supernatant fluid. Appropriate narrow test tubes must be employed in order to permit careful removal of the supernatant fluid and to prevent evaporation of the residual fluid. It is important to have the extract entirely free from debris.

SUMMARY

Increasing sensitivity results from the use of diminishing final concentrations of erythrocytes in the reaction of iso-agglutination. For the detection of traces of agglutinin, the concentrations of red cells usually advocated are excessive and insensitive. Final concentrations of 0.0625 per cent are eight times as sensitive as the usual 0.5 to 1 per cent suspensions and concentrations of less than 0.007 per cent are thirty-two times as sensitive.

If maximum sensitivity is desired, it is necessary to use extremely small quantities of erythrocytes and a great excess of serum. The practical use of such a combination is made possible by a technic of centrifugation and secondary diminution of serum volume.

The advantage of using this technic in determining the presence of iso-agglutinin in dried blood stains and thereby confirming the results of absorption tests has been demonstrated.

HYPERTROPHY AND HYPERPLASIA OF THE ISLETS OF LANGERHANS OF THE FETUS AND OF THE NEWBORN INFANT

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Hypertrophy and hyperplasia of the islands of Langerhans in the pancreas of the newborn infant were first described by Dubreuil and Anderodias,[1] in 1920. They stated that the mother of the infant exhibited glycosuria of pregnancy, and they considered the change in the fetal pancreas a result of disturbance in maternal sugar metabolism.

Since 1921 there have been reported 24 instances of similar findings in pancreases of newborn infants of mothers who are stated to have had diabetes mellitus. The original case of Dubreuil and Anderodias is usually considered to have also been one of diabetes mellitus, although the authors did not make such a statement.

There was no suggestion that the condition might occur in the absence of maternal diabetes until 1937, when Hartmann and Jaudon [2] reported such a case found during an intensive investigation of clinical hypoglycemia in infants. To our knowledge only 4 other cases have been reported in which an excessive amount of islet tissue has been observed in infants born of nondiabetic mothers.

We have found this condition on several occasions during the last few years and have felt that in view of the almost universal acceptance of increase in islet tissue as a phenomenon due directly to maternal diabetes, its occurrence in infants of nondiabetic mothers should be emphasized.

We have therefore reviewed the cases in the literature in which an increase in the number and size of the islands of Langerhans in the

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1. Dubreuil, G., and Anderodias: Compt. rend. Soc. de biol. **83**:1490, 1920.

2. Hartmann, A. F., and Jaudon, J. C.: J. Pediat. **11**:1, 1937.

*Summary of Cases of Hypertrophy and Hyperplasia of Pancreatic Islands in Newborn Infants (Modified and Amplified from Roscoff, Beilly and Jacobi [Am. J. Dis. Child. **55**:330, 1938] and Bauer and Royster [Bull. Ayer Clin. Lab., Pennsylvania Hosp. **3**:109, 1937])*

Case	Authors *	Condition of Mother: Age, Year	Condition of Mother: Deliveries	Condition of Mother: Metabolic Disorder	Clinical Course of Newborn	Birth Weight, Gm.	Lowest Blood Sugar, Mg. in 100 Cc.	Microscopic Appearance of Pancreas: General	Microscopic Appearance of Pancreas: Islands per 50 Sq. Mm.†	Microscopic Appearance of Pancreas: Island Size or Diameter, Microns §	Other Observations at Autopsy and Contributory Causes of Death
					GROUP A						
1	Wiener, H. J.: Am. J. Obst. & Gynec. **7**: 710, 1924	24	..	Severe diabetes for 3 years	Premature, stillborn	1,900	.....	Islets surrounded by edematous connective tissue; some islets larger than normal; cells edematous	.....	.....	.....
2	Gray, S. H., and Feemster, L. C.: Arch. Path. **1**: 348, 1926	44	6	Severe diabetes for 15 yr.; improved at the end of pregnancy; died of toxemia	Premature, at 8th mo.; died on third day of life	3,300	3d day: 67.....	Hypertrophy and hyperplasia of islands (24 times normal size)	184	213 x 182	Hemorrhage and necrosis of adrenals: medulla hypertrophic
3	Schretter, G., and Nevinny, H.: Arch. f. Gynäk. **143**: 465, 1930	38	8	Severe diabetes for 1 year	Spontaneous delivery; died on 32d day of congenital heart disease	4,750	At birth: 62 5½ hr. after: 52 5th day: 62 16th day: 172	Hypertrophy and hyperplasia of islands; islet cell nuclei hyperchromatic, giant, swollen; lipoid droplets in some	Increased (esp. in tail)	Larger than normal (giant islands)	Eosinophilic cells of pituitary increased in number; defect of ventricular septum, anomaly of arteria pulmonalis
4	Bowen, B. D., and Heilbrun, N.: Am. J. M. Sc. **183**: 803, 1932 (case 5)	26	1	Severe diabetes for 3 yr.; improved at mid-pregnancy; later coma	Following cesarean section at term, infant lived only a few hours	.....	.....	Hypertrophy of islands (no details)	.....	.....	.....
5	Nothmann, M., and Hermstein, A.: Arch. f. Gynäk. **150**: 287, 1932. Heiberg, K. A.: Virchows Arch. f. path. Anat. **287**: 629, 1933	28	3	Severe diabetes for 5 yr.; impaired during pregnancy	Spontaneous delivery ms. 8th; died on 2d day with severe cyanosis	3,650	Half hour after birth: 70; 2 hr. after birth; 68	Hypertrophy of islands (total weight of pancreas 5 Gm., i. e., almost 3 times normal)	No increase	Tail: 180-195 Middle: 150 Head: 210	Bronchopneumonia; hemorrhages in pia mater cerebri
6	Skipper, E.: Quart. J. Med. **2**: 353, 1933 (case 9, II)	23	2	Severe diabetes for ½ yr.; juvenile myxedema	Cesarean section at term; died within a few minutes	4,500	.....	Hypertrophy of islands (no details)	.....	.....	.....
7	Skipper (case 22)	32	1	Severe diabetes for 2½ years	Cesarean section at term; died within 3 hours	2,880	.....	Hypertrophy of islands (no details)	.....	.....	.....
8	Jacobsen, N. S.: Ugesk. f. læger **96**: 347, 1934	30	1	Severe diabetes for 9 years	Spontaneous delivery; stillborn	4,700	.....	Hypertrophy and hyperplasia of islands	280 (head)	64-280 (head)	Adrenals large, with narrow medulla and central autolysis and hemorrhage
9	Ehrich, W.: Klin. Wchnschr. **13**: 584, 1934	34	2	Mild diabetes; slightly impaired during pregnancy	Cesarean section; died in convulsions after 12 hours	3,100	.....	Hypertrophy and hyperplasia of islands	Increased	Max. 500 to 600	Insulin given post partum; hemorrhagic skin blisters; partial atelectasis of lungs; adrenals and thyroid normal

9	Ehrlich, W.: Klin. Wchnschr. **13**: 584, 1934	34	2	Mild diabetes; slightly impaired during pregnancy	Cesarean section; died in convulsions after 13 hours	3,100	.....	Hypertrophy and hyperplasia of islands	Increased	Max. 500 to 600	Insulin given post partum; hemorrhagic skin blisters; partial atelectasis of lungs; adrenals and thyroid normal
10	Gordon, W. H.: J. Michigan M. Soc. **34**: 167, 1935; Ohio State M. J. **32**: 540, 1936 (case 1)	29	9	Severe diabetes for 8 yr.; died in coma before delivery	Antepartum death at 8th month	"Large"	.....	In all 4 cases (nos. 10 to 13 inclusive): hypertrophy and hyperplasia of islands; amount of islet cell tissue 6-8 times normal; marked infiltration of eosinophilic cells, in and around island cells; individual cells often large	Increased	Increased	Sugar and acetone in fetal urine
11	Gordon (case 2).....	24	1	Uncontrolled diabetes for 10 yr.	Cesarean section; died 12 hr. after birth	2,510	Heart blood post mortem too low to read	.....	Increased	Increased	Adrenals somewhat atrophic; thymus larger than normal
12	Gordon (case 3).....	39	..	Uncontrolled diabetes	Cesarean section at 8½ mo.; died 14 hr. after birth	4,800	At birth: 70 post mortem; 40	.....	Increased	Increased	Thymus half normal size; pituitary and thyroid normal
13	Gordon (case 4).....	23	1	Severe diabetes for 5 years	Spontaneous delivery, premature; died after 28 hours	2,040	Placental: 30 17 hr. post mortem: too low to read	.....	Increased	Increased	In all 4 cases liver cells vacuolated (glycogen?)
14	Sisson and White[5] (case 1)	..	..	Diabetes	.....	.....	.....	Hyperplasia of islands (no details)	.....	.....	.....
15	Sisson and White (case 2)	..	..	Diabetes	.....	.....	.....	Hyperplasia of islands (no details)	.....	.....	.....
16	Angyal, F.: Centralbl. f. allg. Path. u. path. Anat. **66**: 209, 1936	28	2	Severe diabetes for 8 yr.; much improved since 3d mo. of pregnancy	Stillbirth, premature 8 months	2,900	.....	Pancreas 3.3 Gm.; hypertrophy of islands, with nuclei of island cells twice the normal size	133	Av. 172 x 154	Pulmonary atelectasis; hemorrhages due to anoxemia
17	Bauer, J. T., and Royster, H. A.: Bull. Ayer Clin. Lab., Pennsylvania Hosp. **3**: 109, 1937	39	5	Mild diabetes (colored woman) blood pressure 174/104	Spontaneous delivery; premature 8 mo.; tetany; died on 2d day	1,940	Heart blood 5 min. post mortem: 24	Hyperplasia of islands in head and tail of pancreas	Increased	Max. 390 x 330 Min. 50 x 30 Av. 135 x 109	Very mild pneumonia; number of eosinophils in anterior lobe of pituitary increased
18	Okkels, H., and Brandstrup, E.: Acta path. et microbiol. Scandinav. **15**: 268, 1938 (case 1)	..	..	Diabetes with considerable hyperglycemia	Spontaneous delivery; died 4 days after birth	4,050	.....	Pancreas 3.8 Gm.; hypertrophy and hyperplasia of islands	225	Max. 500 Min. 100	Number of eosinophils in anterior lobe of pituitary increased
19	Okkels and Brandstrup (case 2)	..	..	Diabetes with considerable hyperglycemia	Spontaneous delivery; died shortly after birth	Full	.....	Hypertrophy and hyperplasia of islands	296	Max. 900 Min. 100	Number of eosinophils in anterior lobe of pituitary increased

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Case	Authors [a]	Condition of Mother: Age, Year	Condition of Mother: Deliveries	Condition of Mother: Metabolic Disorder	Clinical Course of Newborn	Birth Weight, Gm.	Lowest Blood Sugar, Mg. in 100 Cc.	Microscopic Appearance of Pancreas: General	Microscopic Appearance of Pancreas: Islands per 50 Sq. Mm.†	Microscopic Appearance of Pancreas: Island Size or Diameter, Microns §	Other Observations at Autopsy and Contributory Causes of Death
				GROUP A—(Continued)							
20	Okkels and Brandstrup (case 3)	..	..	Diabetes with considerable hyperglycemia	Spontaneous delivery; premature twin; died shortly after birth	950	.....	Hypertrophy and hyperplasia of islands; pancreas 1.77 Gm.	210	Max. 300 Min. 50	.....
21	Helwig [3] (case 5)....	34	1	Moderate diabetes for 8½ years	Cesarean section at full term; died 9½ hr. after birth	3,020	Cord blood: 130 heart blood post mortem; 60	Hypertrophy and hyperplasia of islands; pancreas 3 Gm.; "mean area" of islands §§ 57,017 sq. microns; eosinophilic infiltration	Increased	Max. 439 x 385 Med. 285 x 239 Min. 115 x 115	Lungs atelectatic; aspiration of amniotic fluid
22	Helwig [3] (case 6)...	37	6	Moderate diabetes for several years	Cesarean section at full term; died 14 hr. after birth	3,500	Cord blood: 100 post mortem: 120 12 hr. post partum: 60	Hypertrophy and hyperplasia of islands; "mean area" of islands 76,183 sq. microns §§; eosinophilic infiltration	Increased	Max. 554 x 462 Med. 254 x 231 Min. 108 x 100	Lungs atelectatic; aspiration of amniotic fluid
23	Helwig [3] (case 8)...	39	14	Mild diabetes (glycosuria of pregnancy?)	Spontaneous delivery at full term; died 60 hours after birth	3,930	48 hr. post partum: 42	Hypertrophy and hyperplasia of islands; pancreas 2 Gm.; "mean area" of islands 60,372 sq. microns	Increased	Max. 539 x 385 Med. 231 x 216 Min. 108 x 92	Thrombosis and acute focal necrosis of one adrenal; heart 38 Gm.
24	Helwig [3] (case 9)...	36	1	Moderate diabetes for 10 years	Cesarean section at full term; born dead	4,540	Cord blood: 120 heart blood post mortem 190	Hypertrophy and hyperplasia of islands; "mean area" of islands 186,637 sq. microns; eosinophilic infiltration	Increased	Max. 662 x 585 Med. 524 x 385 Min. 169 x 154	.....
25	Potter, Seckel and Stryker (case 1)	29	1	Mild diabetes for 10 yr.; no symptoms for last 9 years	Spontaneous delivery at 8 mo.; died 2 hr. after birth	1,820	.....	Hypertrophy and hyperplasia of islands; pancreas 4 Gm.; lymphocytic infiltration	Increased	250-300	Hemorrhages due to anoxemia; adrenals, thyroid and thymus normal
26	Potter, Seckel and Stryker (case 2)	37	2	Diabetes diagnosed during present pregnancy	Spontaneous delivery at full term; born dead	2,995	.....	Hypertrophy and hyperplasia of islands	Increased	Max. 400 Majority 250-300	Adrenals, thyroid and thymus normal; premature separation of placenta

				nancy							separation of placenta
						GROUP B					
27	Dubreuil and Anderodias [1]	32	4	Glycosuria of pregnancy	Lived only few minutes following induced labor at term	5,050	.....	Hypertrophy and hyperplasia of islands (20-30 times normal amounts of islet tissue); some hypertrophic cells with double nuclei	.....	Max. 394 x 335 Min. 206 x 129 Av. 290 x 212	Liver 250 Gm.
28	Rascoff, H.; Beilly, J. S., and Jacobi, M.: Am. J. Dis. Child. 55 : 330, 1938	..	3	No glycosuria; "diabetic" dextrose tolerance curve	Difficult delivery at full term; died after 13 hours	5,280	3 hr. post partum: 27	Hypertrophy and hyperplasia of islands (4-6 times normal amount); eosinophilic infiltration	Increased	Increased	Unilateral adrenal hemorrhage
29	Potter, Seckel and Stryker (case 3)	40	14	Glycosuria of pregnancy; obesity (90 Kg.)	Spontaneous delivery at full term; died on 4th day	5,200	.....	Hypertrophy and hyperplasia of islands	Increased	Max. 320	Severe dehydration; right adrenal hemorrhage
						GROUP C (1)					
30	Hartmann, A. F., and Jaudon, J. C.[2]	..	..	Normal	Spontaneous delivery at full term; died on 3d day with convulsions, cyanosis	5,140	.....	Hypertrophy and hyperplasia of islands	Increased	Increased	.....
31	Helwig [3] (case 9, series 2)	40	3	Normal; slight toxemia of pregnancy	Spontaneous delivery; breathing difficulties; died after 42 hours	4,060	.....	Hypertrophy and hyperplasia of islands; "mean area" of islands 35,715 sq. microns	Increased	Max. 634 x 147 Med. 162 x 139 Min. 85 x 77	.....
32	Potter, Seckel and Stryker (case 4)	23	3	Normal	Stillbirth; premature detachment of placenta	1,740	.....	Hypertrophy and hyperplasia of islands (see text)	Increased	100 to 300	Petechial hemorrhages of thoracic viscera
33	Potter, Seckel and Stryker (case 5)	42	4	Normal	Stillbirth; premature detachment of placenta	2,575	.....	Hypertrophy and hyperplasia of islands (see text)	Increased	80 to 250	Petechial hemorrhages of thoracic viscera
34	Potter, Seckel and Stryker (case 6)	38	13	Normal	Stillbirth; premature detachment of placenta	4,930	.....	Hypertrophy and hyperplasia of islands (see text)	Increased	100 to 300	petechial hemorrhages of thoracic viscera
35	Potter, Seckel and Stryker (case 7)	39	5	Normal	Intrapartum death from cord entanglement; intrauterine pneumonia	3,760	.....	Hypertrophy and hyperplasia of islands (see text)	Increased	Max. 300	Intrauterine pneumonia
36	Potter, Seckel and Stryker (case 8)	19	1	Normal	Premature; died at age of 36 days	2,250	.....	Hypertrophy and hyperplasia of islands (see text)	Increased	Max. 300	Congenital cardiac defect

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Case	Authors *	Condition of Mother: Age, Year	Condition of Mother: Deliveries	Condition of Mother: Metabolic Disorder	Clinical Course of Newborn	Birth Weight, Gm.	Lowest Blood Sugar, Mg. in 100 Cc.	Microscopic Appearance of Pancreas: General	Microscopic Appearance of Pancreas: Islands per 50 Sq. Mm.†	Microscopic Appearance of Pancreas: Island Size or Diameter, Microns §	Other Observations at Autopsy and Contributory Causes of Death
					GROUP C (1)—Continued)						
37	Potter, Seckel and Stryker (case 9)	27	4	Normal	Stillbirth; intrapartum death	4,140	.....	Hypertrophy and hyperplasia of islands (see text)	Increased	Max. 300	.....
38	Potter, Seckel and Stryker (case 10)	39	6	Normal	Stillbirth; intrapartum death	3,300	.....	Hypertrophy and hyperplasia of islands (see text)	Increased	Max. 350	Intracranial hemorrhage
39	Potter, Seckel and Stryker (case 11)	38	2	Normal	Stillbirth; difficult shoulder delivery	4,350	.....	Hypertrophy and hyperplasia of islands (see text)	Increased	Max. 320	.....
					GROUP C (2)						
40	Liebegott, G.: Beitr. z. path. Anat. u. z. allg. Path. **101**: 319, 1938 (case 3)	..	..	Normal	Congenital hydrops; stillbirth	.....	.....	Hypertrophy and hyperplasia of islands; very large cells, nuclei increased in size, some giant	Increased	Increased	.....
41	Liebegott (case 1)..	38	6	Normal	Congenital hydrops; stillbirth 8th month	2,000	.....	Hypertrophy and hyperplasia of islands (same as foregoing case)	Increased	Increased	Congenital hydrops; zona retic. of adrenal cortex widened, fatty infiltration
42	Liebegott (case 2)..	33	7	Normal	Congenital hydrops; stillbirth 8th month	3,000	.....	Hypertrophy and hyperplasia of islands (same as foregoing case)	Increased	Increased	Congenital hydrops; zona retic. of adrenal cortex widened, fatty infiltration
43	Potter, Seckel and Stryker (case 12)	37	6	Normal	Jaundiced; died at 8½ hour of age	3,400	.....	Hypertrophy and hyperplasia of islands (see text)	Increased	Max. 400	Erythroblastosis
44	Potter, Seckel and Stryker (case 13)	28	2	Normal	Jaundiced; died on 3d day	3,905	.....	Hypertrophy and hyperplasia of islands (see text)	Increased	Max. 350	Erythroblastosis
45	Potter, Seckel and Stryker (case 14)	29	4	Normal	Mild hydrops; died at ½ hour of age	2,360	.....	Hypertrophy and hyperplasia of islands (see text)	Increased	Max. 350	Erythroblastosis

* Feldman's case (Centralbl. f. allg. Path. u. path. Anat. **42**: 435, 1928) was not included because no true proliferation of islet tissue was present.

† The normal figure is 60 islands per 50 sq. mm. (Gray, S. H., and Feemster, L. C.: Arch. Path. **1**: 848, 1926).

§ The normal figures in microns are (Dubreuil and Anderodias;[4] Gray and Feemster; Heiberg, respectively):

Maximum,	147 × 126	98? × 126	
Minimum,	64 × 55	85 × 50	
Average,	115 × 105	110 × 105	115 × 118

§§ The normal average figure for island size is 15,800 square microns.

pancreas of a newborn infant was described; on the basis of these and 14 others which we have ourselves observed, we have attempted to evaluate the significance of an increased amount of islet tissue.

Our own cases with a single exception (case 3 is from the Department of Pathology of the University of Chicago) were discovered during routine microscopic examination of 450 pancreases from nonmacerated fetuses, premature infants and infants born at term examined at autopsies in the Department of Obstetrics and Gynecology of the University of Chicago. This series included 4 infants born of diabetic mothers and 22 infants suffering from erythroblastosis.

The cases from the literature together with those of our series have been divided into four groups and are listed in the accompanying table. Group A includes 24 previously reported and 2 newly reported infants all of whom are stated to have been born of diabetic mothers. Group B includes 3 infants, 2 of whom were previously reported, born of mothers who may have had diabetes, though the diagnosis was never definitely established. In group C are 16 infants whose mothers had no history of diabetes and no glycosuria or other clinical evidence of the condition during pregnancy. The last group has been subdivided into (1) 10 infants without associated erythroblastosis (2 previously reported and 8 from our series) and (2) 6 infants with erythroblastosis (3 previously reported and 3 from our series).

The material of principal interest has been briefly presented in the table, and the cases previously reported will not be further discussed. Those presented for the first time are given in more detail immediately following the table.

A. INFANTS BORN OF DIABETIC MOTHERS

CASE 1.—The mother was a 29 year old primipara. Diabetes mellitus had been diagnosed ten years previously, but for nine years no symptoms had been present. The patient was on a diet during the third and succeeding months of pregnancy and for a short time before delivery received 15 units of insulin daily. She went into labor spontaneously at thirty-one weeks and delivered an 1,820 Gm. boy. Respiration was never satisfactorily established, and the infant's heart stopped beating at the end of two hours. At autopsy the body was normal except for the presence of petechial hemorrhages characteristic of anoxemia. The pancreas was normal in gross appearance. Microscopic examination showed an increase in the number and size of the islands of Langerhans, and many measured 250 to 300 microns in diameter. The connective tissue stroma of the lobules was diffusely infiltrated with lymphocytes, mature and immature erythrocytes and granular leukocytes. Large masses of lymphoid cells surrounded many of the major ducts. In the postdelivery examination of the mother, 4 plus reduction was found in the urine, the fasting blood sugar was 210 mg. per hundred cubic centimeters and an oral dextrose tolerance test confirmed the diagnosis of diabetes.

CASE 2.—The mother was a 37 year old woman who had had five previous pregnancies, four of which ended in abortions. A diagnosis of diabetes mellitus was made for the first time during the present pregnancy, three months before

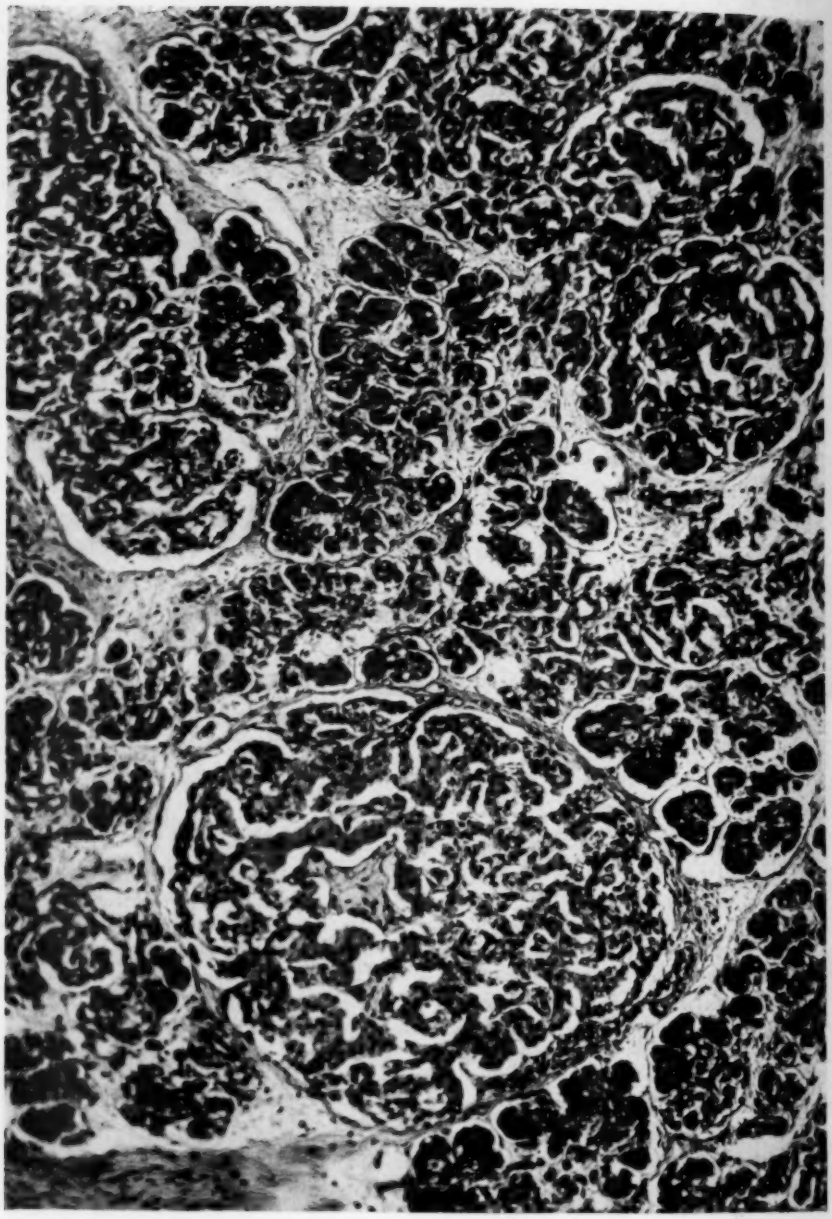

Fig. 1 (case 2).—Section of the pancreas of an infant born of a diabetic mother. This area is typical of the tissue examined and shows an increase in both size and number of islands. Hematoxylin-eosin stain; × 125.

delivery. An oral dextrose tolerance test three weeks before delivery revealed: at the start, a blood sugar level of 160 mg. per hundred cubic centimeters and a trace of reducing substance in the urine; at one-half hour, 238 mg. per hundred cubic centimeters and 1 plus reduction; at one hour, 270 mg. and 4 plus reduction; at two hours, 240 mg. and 4 plus reduction, and at three hours, 158 mg. and 4 plus reduction. She was admitted to the hospital at forty weeks' gestation because of vaginal bleeding. A diagnosis of premature separation of the placenta was made; the fetal heart tones disappeared one hour before delivery. The fetus weighed 2,995 Gm. and evidenced no gross abnormalities other than extreme congestion of the viscera. On microscopic examination the pancreas showed a considerable increase in the size and number of islands of Langerhans. Many of the islands measured from 250 to 400 microns in diameter (fig. 1). There was a mild diffuse infiltration of immature erythrocytes and leukocytes in the connective tissue stroma. The dextrose tolerance test was repeated one week after delivery, and the diagnosis of diabetes mellitus was confirmed.

B. INFANT BORN OF MOTHER WITH MILD METABOLIC DISTURBANCE PROBABLY NONPANCREATIC IN ORIGIN

CASE 3.—The mother was an obese woman 40 years of age, who had had thirteen previous pregnancies. In the fifth and eighth months of the present pregnancy a 4 plus reduction was found in her urine, while two tests in the sixth and two in the ninth month revealed only traces or absence of sugar. Delivery of a 5,200 Gm. boy occurred at forty weeks' gestation. The infant regurgitated its food from the second day of life and on the third day was extremely dehydrated, with a temperature of 100 F. On the fourth day he was brought to the hospital but was dead on arrival. At autopsy the body weighed 3,590 Gm. A massive right adrenal hemorrhage was found, with a retroperitoneal hematoma and hemoperitoneum. The pancreas was normal in size and shape, but on microscopic examination the islands of Langerhans were found increased in size and number. Several of the islands measured 320 to 360 microns in diameter, although the majority were somewhat smaller (fig. *2A*). Five months after delivery, the mother weighed 89.7 Kg. (height, 137 cm.). The urine was sugar free. In an oral dextrose tolerance test the blood sugar during the fasting period was 107 mg. per hundred cubic centimeters, with no urine reduction; at one-half hour, 128 mg. and no reduction; at two hours, 179 mg. and sugar (1 plus) in the urine, and at three hours, 129 mg. and a trace of sugar in the urine. The curve indicates a decreased tolerance for dextrose; this was believed to be nonpancreatic in origin and due probably to some other metabolic disturbance.

C. INFANTS BORN OF MOTHERS WITHOUT DEMONSTRABLE METABOLIC DISTURBANCES

1. *Infants Without Erythroblastosis.*

CASE 4.—The mother was a 23 year old woman who had had two previous pregnancies. The present pregnancy was uneventful until after the onset of labor, when hemorrhage occurred, and a diagnosis of premature detachment of the placenta was made. The urine at no time contained sugar. The fetal heart tones disappeared before delivery. At autopsy the fetus weighed 1,740 Gm.; the only gross abnormalities found were those associated with anoxemia. The greater part of the pancreatic tissue was composed of masses of hypertrophic islands, with acini present only in small irregular groups. The islands were

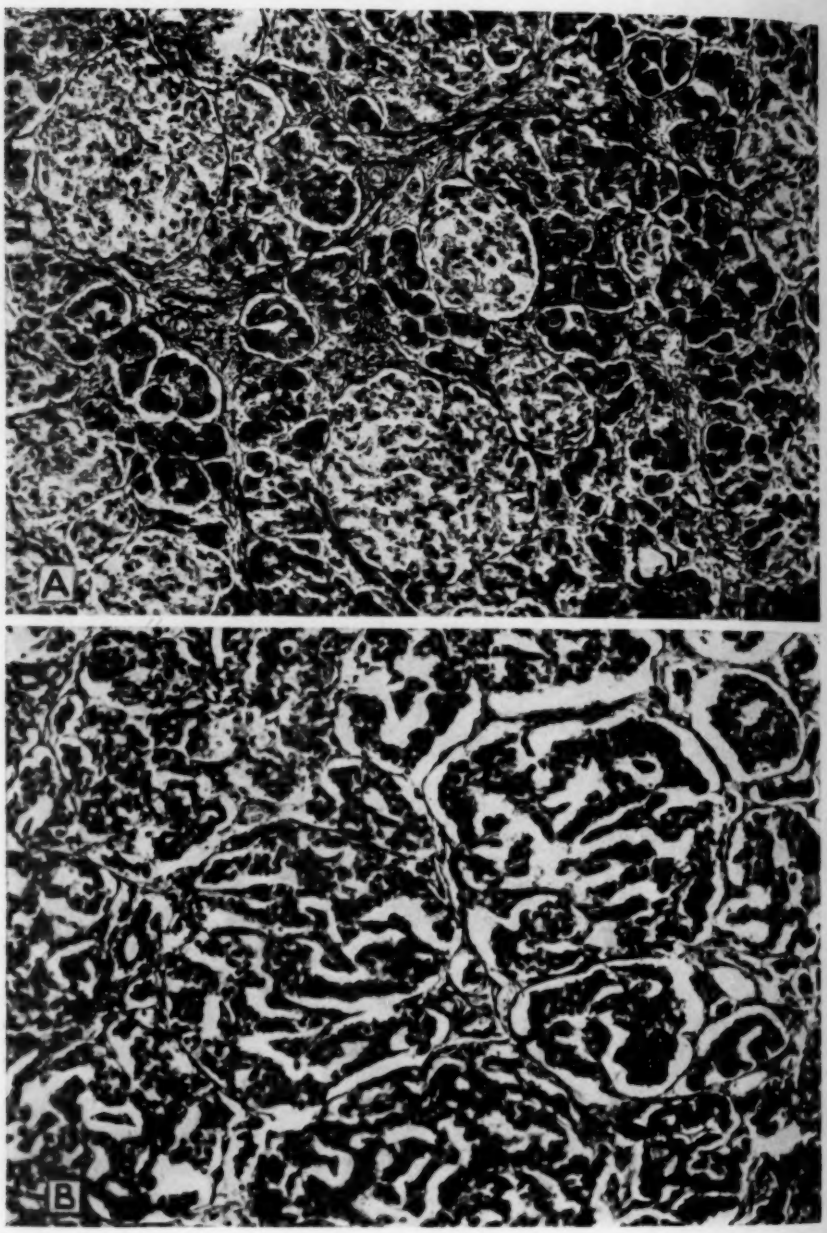

Figure 2

(See legend on opposite page)

congested, and in some areas the capillaries had ruptured. The islands varied in diameter from 100 to 400 microns. Occasional immature blood cells were present in the stroma.

CASE 5.—The mother was 42 years of age and had had three previous pregnancies, one of which terminated in the delivery of a stillborn fetus. The present pregnancy was uneventful; the urine contained no sugar. The fetal heart tones disappeared during labor as a result of premature detachment of the placenta. The fetus at autopsy weighed 2,575 Gm. and showed no gross abnormalities except those associated with intrauterine anoxemia. The pancreas was composed largely of islet tissue. The islands varied in diameter from 80 to 250 microns and for the most part were massed in the centers of the lobules, with only a small amount of acinar tissue about the periphery (fig. 2*B*). Normoblasts were scattered through the connective tissue stroma.

CASE 6.—The mother was 38 years of age and had had twelve previous pregnancies, all ending with the delivery of normal living infants. This pregnancy was uneventful until delivery, when a diagnosis of premature detachment of the placenta was made. The urine had been entirely sugar free. The fetal heart tones disappeared during labor. At autopsy the fetus weighed 4,930 Gm., and the examination disclosed no abnormalities except the petechial hemorrhages of the heart, thymus and lungs associated with anoxemia. The pancreatic islands were increased in number and size, individual islands measuring up to 300 microns. They were distributed throughout the lobules, part being central and part peripheral with acini filling the remaining spaces. Normoblasts and a few immature leukocytes were present in the connective tissue.

CASE 7.—The mother was 39 years of age and had had four previous normal pregnancies. The pregnancy was normal and the urine was sugar free on all examinations. Her weight was 221 pounds (100 Kg.) at the time of conception, and she gained moderately throughout pregnancy. Fetal death occurred during delivery, presumably from strangulation of the cord. The fetus weighed 3,760 Gm. Microscopic examination revealed intrauterine pneumonia. Although they did not appear greatly increased in number, the islands of Langerhans showed extreme hypertrophy. Many measured from 250 to 300 microns in diameter. The acinar tissue was proportionately reduced. The connective tissue stroma was densely infiltrated with plasma cells, eosinophils and lymphocytes (fig. 3*A*).

CASE 8.—The mother was a primipara 19 years of age. Pregnancy was entirely uneventful, and the urine was sugar free on all examinations. Labor occurred at thirty-five weeks' gestation, and a 2,260 Gm. boy was delivered. A systolic murmur was audible at birth, and the condition of the infant was poor and remained so until death occurred, on the thirty-sixth day. Autopsy disclosed a congenital cardiac defect. The pancreas was grossly normal. Micro-

EXPLANATION OF FIGURE 2

A (case 3), section of the tail of the pancreas of an infant born of a mother with glycosuria of pregnancy. There is marked hyperplasia of islet tissue, with hypertrophy of the individual islets. Mallory's connective tissue stain; × 125. *B* (case 5), section of the pancreas of an infant born of a normal nonglycosuric mother. The area shown consists almost entirely of island tissue and is typical of the sections examined. Hematoxylin-eosin stain; × 125.

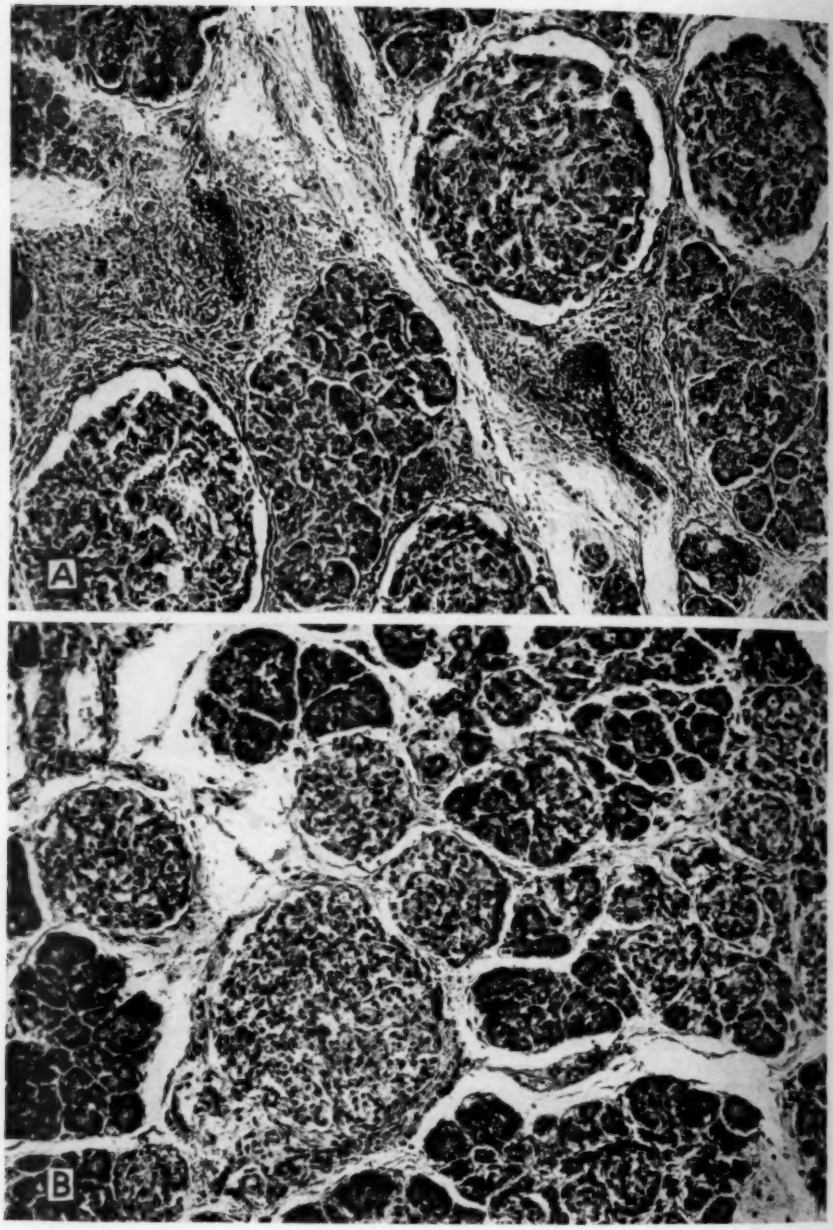

Figure 3

(See legend on opposite page)

scopically there were marked hyperplasia and hypertrophy of the islands of Langerhans and infiltration of connective tissue by lymphocytes. The islands measured up to 300 microns in diameter.

CASE 9.—The mother was a 27 year old Negress who had had three previous normal pregnancies. This pregnancy also was uneventful, and the urine at no time contained sugar. A girl weighing 4,140 Gm. was delivered at term, death taking place during labor. A definite cause of death could not be determined. The pancreas was the only organ showing any abnormality; the majority of the islands were increased in size, many measuring 250 to 300 microns in diameter.

CASE 10.—The mother was 39 years of age and had had five previous pregnancies, two of which ended in abortions. This pregnancy was uneventful, and the urine was sugar free on all examinations. A 3,300 Gm. girl was delivered at term. The heart tones disappeared ten minutes before delivery. Autopsy disclosed a moderate subtentorial hemorrhage. The pancreas contained numerous giant islands 300 to 350 microns in diameter.

CASE 11.—The mother was 38 years of age and had had one previous normal pregnancy. This pregnancy was uneventful; the urine was sugar free on all examinations. Delivery of a 4,340 Gm. boy occurred at term. The heart ceased beating during a difficult extraction of the shoulders. No abnormalities were found at autopsy except in the pancreas. The islands were increased in number, and many were definitely enlarged, measuring up to 320 microns in diameter.

2. *Infants with Erythroblastosis.*

CASE 12.—The mother was 37 years of age and had had five previous pregnancies, two of which terminated in abortions. This pregnancy was uneventful; the urine was sugar free. A 3,400 Gm. boy was delivered thirty-one weeks after the onset of the last menstrual period. He was deeply jaundiced at birth and succumbed at 8½ hours of age. Microscopic examination revealed the presence of erythroblastosis. The pancreas contained extremely numerous prominent islands, many measuring as much as 350 to 400 microns in diameter. Marked erythropoiesis was present (fig. 3 *B*).

CASE 13.—The mother was 28 years of age and had had one previous normal pregnancy. This pregnancy was uneventful and the urine at all times was sugar free. A 3,905 Gm. girl was delivered at term. She became deeply jaundiced within twenty-four hours after birth and despite repeated blood transfusions died on the third day of life. An increase in number and size of the islands was present. Many measured over 300 microns in diameter. All tissues, including the pancreas, were typical of erythroblastosis.

CASE 14.—The mother was 29 years of age and had had three previous pregnancies, the last two of which ended in abortions. The present pregnancy was uneventful except for an occasional trace of albumin in the urine. All specimens

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EXPLANATION OF FIGURE 3

A (case 7), section of pancreas of an infant born of a nondiabetic mother. The islands are large and isolated by bands of connective tissue containing numerous immature leukocytes. Syphilis and erythroblastosis were excluded as contributing factors. Hematoxylin-eosin stain; × 125. *B* (case 12), section of pancreas of an infant with erythroblastosis, born of a nondiabetic mother. Hematoxylin-eosin stain; × 125.

were sugar free. A boy weighing 2,360 Gm. was delivered at thirty-six weeks' gestation. Difficulty in establishing respiration was encountered, and the heart ceased beating thirty minutes after birth. The infant was only slightly edematous, but the histologic appearance of the organs was characteristic of erythroblastosis. The pancreas showed a definite increase in the size and number of islands. Many measured as much as 350 microns in diameter.

COMMENT

True diabetes mellitus was present in the mother in 24 cases previously reported in which an increased amount of pancreatic islet tissue was present in a fetus or a newborn infant as a result of an increase in the number of islands, an increase in the size of the islands or of both. Two similar cases of our series are added, making a total of 26. Thus there is, in some instances, a definite association of maternal diabetes with increased islet tissue in the fetal pancreas, but as yet no entirely satisfactory explanation for this phenomenon has been advanced. The amount of islet tissue has no constant relation to the severity or the state of control of the maternal diabetes, nor is the amount of islet tissue demonstrable at autopsy consistent with the blood sugar levels determined in the infants before death.[3] It has been believed that the stimulation of the fetal pancreas compensates to some extent for the lack of insulin in the maternal tissues,[4] but in only 3 cases of the entire series was the mother noticeably improved during pregnancy. In the large majority the symptoms were stationary or intensified. Also of note is the observation that the offspring of mothers with diabetes frequently fail to show islet hypertrophy or hyperplasia even when the diabetes is severe and uncontrolled. Sisson and White[5] found increased number and size of islands in only 2 of 8 infants born of diabetic mothers and examined at autopsy.[6] Helwig[3] reported abnormal findings in 4 of 9 examined, and in our series there were only 2 with islet increase out of 4 such infants coming to autopsy.

Experimental work with pregnant depancreatized bitches has in some instances appeared to indicate that sufficient insulin might be produced by the fetal pancreas to control maternal carbohydrate metabolism (Carlson and co-workers[4]) but has failed to do so in other experiments (Markowitz and Soskin[7]; Allen[8]).

Increased islet tissue has been postulated as the cause of death in infants born of diabetic mothers on the basis that when the maternal source of carbohydrate is withdrawn a relative hyperinsulinism with

3. Helwig, E. B.: Arch. Int. Med. **65**:221, 1940.

4. Carlson, A. J.; Orr, J. S., and Jones, W. S.: J. Biol. Chem. **17**:19, 1914.

5. Sisson, W. R., and White, P.: Tr. Am. Pediat. Soc. **48**:47, 1936.

6. Subsequently White reported (Arch. Int. Med. **63**:39, 1939) that the finding was present in 3.

7. Markowitz, J., and Soskin, S.: Am. J. Physiol. **79**:553, 1927.

8. Allen, F. M.: Am. J. Physiol. **54**:451, 1921.

resultant hypoglycemia develops. The mechanism regulating the blood sugar in newborn infants, however, is normally unstable, and within short periods of time the level may vary considerably; values as low as 40 mg. per hundred cubic centimeters may be regarded as normal in the first week of life.[9] The blood sugar levels of 11 of the 24 infants in group A, all with increased islet tissue, varied from 0 to 190 mg. per hundred cubic centimeters. In the series discussed by White [10] it was found, when the size of the islands was correlated with the blood sugar findings, that the hyperplasia occurred with normal and with elevated blood sugar values as well as with hypoglycemia. Thus, from the evidence now available, all that may be justifiably concluded regarding the increase in islet tissue in the offspring of diabetic mothers is that in some instances the pancreas during intrauterine life is stimulated so that an abnormal amount of islet tissue develops; but even in those cases in which the islets are hyperplastic there is no positive evidence that the total production of insulin is increased beyond the normal.

The infants described in group B might possibly be included in group A, since the mothers may have had mild or early diabetes. However, because of the possibility that the metabolic disturbance in the mothers was due to some other cause they were separated from those of mothers for whom the diagnosis was definite. In either case the changes in the pancreas occurred in the absence of any marked disturbance in the maternal metabolism.

In group C the 5 infants whose histories are recorded in the literature and the 11 from our material were all infants and fetuses born of mothers in whom no glycosuria or other symptoms of diabetes mellitus were present. One reason for the relatively small number reported previously is doubtless the infrequency with which a microscopic examination is made of the pancreas of an infant other than one in whom a definite abnormality is suspected. The 6 infants with erythroblastosis in group C (2) seem too many for the associated condition to be entirely coincidental, but no explanation is available at this time as to the reason for the association. In practically all infants with erythroblastosis the islets are unusually prominent and appear somewhat larger and more numerous than those in normal infants. In the ones reported here this change was excessive.

In regard to the infants and fetuses without erythroblastosis there is nothing in the maternal history or the results of postmortem examination to suggest an etiologic factor for the increased size of the islands. Premature detachment of the placenta occurred in several of the cases, and it might be postulated that the abnormal detachment was caused by the same toxic condition in the mother which produced islet change in

9. McKittric, J. B.: J. Pediat. **16**:151, 1940. Hartmann and Jaudon.[2] Sisson and White.[5]

10. White, P.: Surg., Gynec. & Obst. **61**:324, 1935.

the fetus. However, a review of the autopsy observations in our entire series of infants who succumbed from anoxia produced by premature placental detachment shows that changes in the islets of Langerhans were present in only a small percentage. There is probably no significance in the association of the two conditions.

The pancreases of the 8 infants and fetuses reported by us which fall in group C (1) were normal in size and gross appearance. In these, as in all pancreases of newborn infants, masses of lymphocytes were present around the secretory ducts, and occasional somewhat immature leukocytes were present in the stroma. Normal islands may measure slightly over 100 microns in diameter, and in all microscopic preparations part of the islands fell within this normal range; all of the preparations in our reported cases, however, contained numerous islets measuring more than 250 microns in diameter, a size definitely abnormal. The islet tissue almost without exception was partially composed of abnormal cells, with irregular giant nuclei variably distributed throughout the cytoplasm, a change similar to that often found in the abnormal islets of infants born of diabetic mothers. It is impossible to differentiate the pancreases of infants of diabetic from those of infants of nondiabetic mothers when hyperplasia and hypertrophy of the islands are present.

It is only by making serial sections of the pancreas and estimating the number and volume of the islets in all parts, or by determining the amount of insulin by chemical assay, that positive information on the state of function of the islets can be obtained. Since this is not possible except in the rare cases in which an abnormal condition is suspected at the time of autopsy, the diagnosis of increased islet tissue must rest on the presence of hypertrophied islets plus an estimated increase in number. Familiarity with the amount of islet tissue normally present at various stages of development is essential for a correct diagnosis.

SUMMARY

Hyperplasia and hypertrophy of the islets of Langerhans of the pancreas of the fetus or the newborn infant may be found in association with maternal diabetes or may be present though the mother is nondiabetic. The condition is occasionally found in infants suffering from erythroblastosis.

In the majority of cases there is no correlation between the increase of islet tissue and the severity of the diabetes, the state of control or the change in sugar tolerance of the mother during pregnancy. There is also little correlation between the amount of islet tissue found at autopsy and the blood sugar levels determined before death in those infants who succumb during the neonatal period. Thus an increased amount of islet tissue may be found in the fetal pancreas in the presence or in the absence of abnormal sugar metabolism in the mother and in the presence or in the absence of abnormal sugar metabolism in the infant itself.

ANATOMIC AND BEHAVIOR CHANGES PRODUCED BY PARTIAL HEPATECTOMY IN THE RAT

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BALTIMORE

The effects produced on the spontaneous activity of rats by ligation of the bile duct were dealt with in a previously published paper (Richter and Benjamin [1]). In one group of rats two ligatures were applied, and the duct was cut between them. Within several weeks the bile duct became greatly distended with fluid, and back pressure destroyed the liver cells, giving a typical picture of biliary cirrhosis with extensive sprouting of small bile ducts and necroses. In another group only one ligature was applied. In all of these rats an outlet through the distal end of the duct ultimately was reestablished. Signs of biliary cirrhosis indicated that during the period of distention the back pressure must have also exerted a temporarily destructive effect on the liver cells in these animals.

Of particular interest was the fact that many of the rats with single ligature and some of the rats with double ligature became more active rather than less active, despite the operative disturbances, and remained hyperactive for several weeks. It was assumed that in some way the increased activity depended on the temporary or permanent disturbances of liver function.

It was decided then to determine whether removal of a large part of the liver would have the same effect on spontaneous activity as the destruction of liver tissue produced by ligation of the bile duct. The recent development by Higgins and Anderson [2] of a simple method for partial hepatectomy made it possible to give an answer to this question. Observations were also made on the effect produced by partial hepatectomy on the endocrine glands, vaginal smears, body weight, and food and water intake.

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1. Richter, C. P., and Benjamin, J. A.: Arch. Path. **18**:817, 1934.
2. Higgins, G. M., and Anderson, R. M.: Arch. Path. **12**:186, 1931.

METHODS

Young female rats were used. Each was placed in a separate activity cage, which consisted of a revolving drum, a cyclometer and a living compartment with a food box (standard McCollum diet) and an inverted graduated water bottle. Daily records were made of activity, food and water intake, and vaginal smears; weekly records were made of body weight. At an average age of 69 days, when in most instances the activity had reached a constant level, partial hepatectomy was performed. Daily observations were continued for the following forty days, the standard length of observation period used in many of our experiments. At the end of this time, when the rats had reached an average age of 109 days, they were killed and examined. The liver and endocrine glands were weighed and preserved for histologic study.

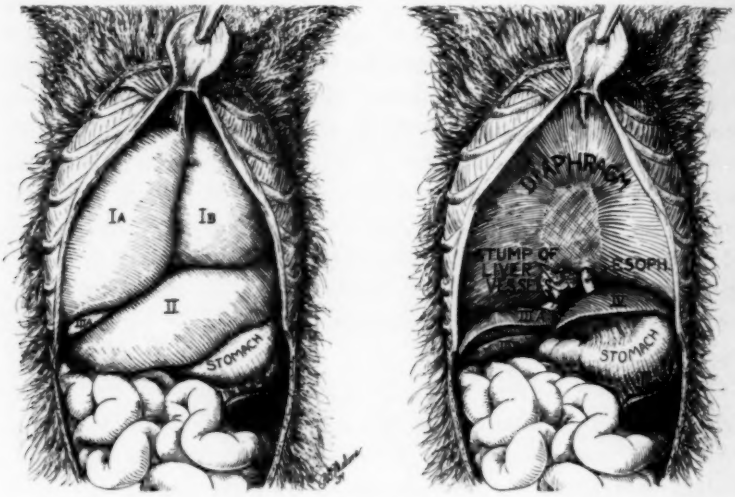

Fig. 1.—Drawing showing the liver of the rat before and after removal of lobes IA, IB and II.

The technic used to remove the liver tissue closely followed the description given by Higgins and Anderson.[2] Figure 1 shows on the left the position of the liver in the abdominal cavity. The right and left median lobes, IA and IB, and the left lateral lobe, II, were exposed through a midline incision; then a loop of linen twist was passed around these three lobes, IA, IB and II, and drawn tight over the vessels at their base, but not involving the portal of hepatic veins. These lobes were then excised with a single cut of a scalpel. Figure 1 on the right shows the stumps of the vessels, the remaining lobes, IIIA, IIIB and IV, and the large cavity left in the abdomen. The incision was closed with a continuous silk suture through the peritoneum and muscles and with interrupted silk sutures through the skin. For the first postoperative night the rats had access only to a 5 per cent dextrose solution and water. On the second day they had access again to the regular McCollum diet and water. We found that the rats could not survive additional removal of the right lateral lobe.

At autopsy the liver and endocrine glands were removed. The livers were prepared for weighing by severing the vessels, dissecting free any adherent tissue and wiping off any blood or other fluid on a gauze sponge.

RESULTS

Amount of Liver Removed and Amount of Regenerated or Hypertrophied Tissue.—The amount of liver tissue removed in the 10 rats averaged 3.9 Gm., or 66 per cent of the average liver weight of rats of the same operative weight, and ranged from 3.4 to 5.3 Gm., or 62 to 76 per cent of the calculated liver weight, with the exception of the tissue removed from 1 rat, which weighed only 2 Gm., or 34 per cent.

At autopsy the liver weights averaged 7.6 Gm., or 4.2 per cent of the average body weight. Since the liver weights of 14 normal rats, killed at approximately the same age, averaged 8.1 Gm., or 4.4 per cent of the average body weight, in forty days the remaining liver had hypertrophied until its total weight reached the average weight for normal rats. The remaining lobes of the liver had hypertrophied; the excised lobes did not regenerate. This agrees with the observations reported by Fishback,[3] Higgins and Anderson [2] and others.

Effect on Activity.—Figure 2 *A* gives a typical record of the activity of 1 rat. The ordinates show the activity in number of revolutions of the drum; the abscissas, age in days. This rat was placed in the activity cage at the age of 48 days and was operated on at the age of 62 days. In the operation 4.4 Gm., or approximately 75 per cent, of the liver was removed. Two days before the operation the activity reached 18,500 revolutions. On the first postoperative day the activity dropped to 200 revolutions; by the fifth day it had increased to 19,300 revolutions, surpassing even its highest preoperative record. Thereafter it increased in irregular bursts and ultimately reached a peak of 28,700 revolutions on the twenty-fifth day after operation. The rat was killed on the fortieth day. Apparently, removal of a large part of the liver made this rat hyperactive rather than hypoactive, in spite of the shock involved in the laparotomy.

Figure 2 *B* shows the average daily activity in ten day periods for the 10 hepatectomized rats. In the ten day period preceding the operation the activity averaged 9,000 revolutions per day. In the first ten day postoperative period the activity dropped to 6,400 and then, in the period between the twentieth and the thirtieth day, increased to 14,500 revolutions. Six of the rats attained levels which were far above their preoperative and the normal averages, while the others maintained their preoperative levels or showed a moderate increase.

3. Fishback, F. C.: Arch. Path. **7**:955, 1929.

These results show that the removal of such large amounts of liver tissue interfered little with spontaneous activity and that, rather than making the rats inactive, it seemed to make them hyperactive. In view of the shock, the loss of blood, the large changes of internal pressure in the abdominal cavity, the incision in the abdominal wall, and other injuries involved in the operation, and the fact that control laparotomy

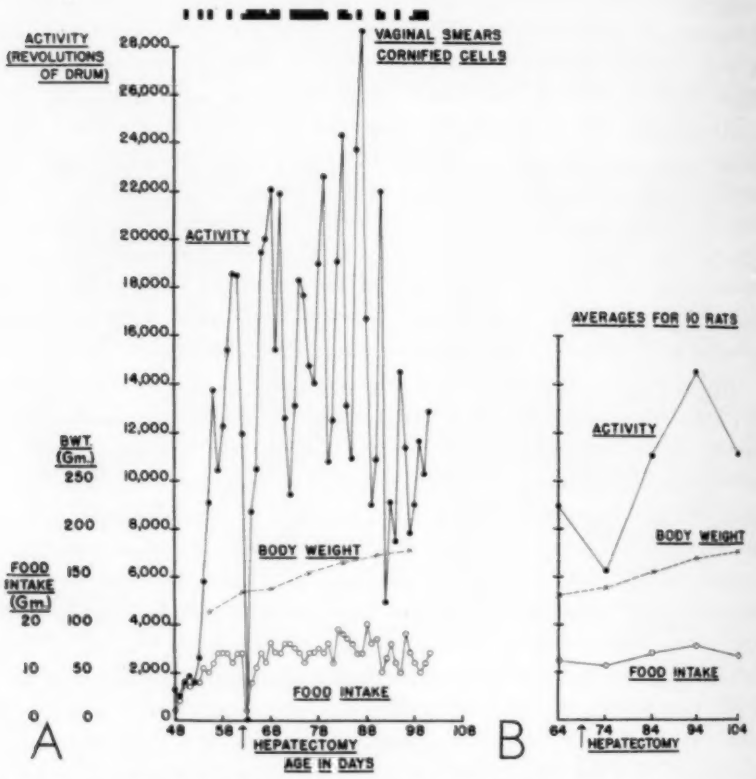

Fig. 2.—*A*, the effect of hepatectomy on the activity of 1 rat. *B*, in averages for the 10 rats, the effects produced by hepatectomy on activity, food intake and body weight.

without removal of any liver produced a greater and more prolonged period of inactivity and no hyperactivity, we feel that the high level of activity of hepatectomized rats must have a special significance.

Effects on Other Functions.—Body Weight: Figure 2 *A* shows a typical body weight curve. During the first ten days after operation the rate of gain decreased slightly. Figure 2 *B* gives the average weight curve for the 10 rats. It closely approximated the normal curve. At an average age of 109 days the 10 rats had an average weight of 179

Gm., while 10 normal rats killed six days earlier weighed only 166 Gm. Clearly, the removal of the liver did not cause the animals to lose weight.

Food Intake: The removal of such a large part of the liver had little effect on food intake, as is shown in figure 2 *A*. The daily food intake decreased only for three days. Thereafter it not only attained but surpassed its preoperative level. As is shown in figure 2 *B*, the average food intake dropped, but only slightly, during the first ten day postoperative period and then surpassed the original level.

Water Intake: The daily water intake increased slightly above the normal average in several of the rats. The intake of 1 rat increased from an average of 21.1 cc. for the last ten day preoperative period to 38 cc. twenty days later. The average curve for the 10 rats closely paralleled the curve for normal rats.

Estrous Cycle and Vaginal Smears: Hepatectomy had a marked effect on the estrous cycle and the vaginal smears. For 4 rats, the four to five day cycle of cornified cells in smears was lengthened to a five or six day cycle. One rat showed six regular six day cycles. However, for most of the rats (6) the four to five day cycle in the smears disappeared altogether, leaving only constant cornification of the vaginal epithelium (see fig. 2 *A*). The relation between activity peaks and the cornification of cells in the vaginal epithelium of normal animals as shown by vaginal smears was lacking in most of these rats. Like vitamin A–deficient rats, the rats with constant cornification of cells in the smears showed fairly regular activity cycles, probably indicating that their ovaries functioned normally and were not affected by the hepatectomy.[4]

Endocrine Glands: The endocrine glands did not deviate in weight significantly from those of normal rats killed at approximately the same age, with the possible exception of the thyroid glands, which were slightly smaller.

COMMENT

In these experiments it was found that hepatectomy made some of the animals more active than they had been before. These results agree with observations made earlier on the effects produced on spontaneous activity by hepatic damage which resulted from temporary obstruction of the common bile duct.[1]

At present no definite explanation of these results suggests itself. The failure of partial hepatectomy to produce a depressive effect on activity, food or water intake, or body weight indicates that the liver must serve primarily as a storage depot and that it does not take an active part in the final metabolic function of the body. It is possible that the increased activity found in some of the animals helped to

4. Richter, C. P., and Barelare, B., Jr.: Endocrinology **24**:364, 1939.

metabolize sugar and other substances which, owing to the removal or destruction of a large part of the liver, could no longer be stored and, hence, appeared in other parts of the body in excessively large amounts. The increased activity would then be regarded as a part of the mechanism by means of which the organism maintained a constant internal environment.

Since the liver serves as the chief storage depot for vitamin A, it is conceivable that removal of part or all of the liver might bring out symptoms of vitamin A deficiency. We might, therefore, regard the appearance in a number of the animals of constant cornification of the cells of the vaginal epithelium, one of the first symptoms of vitamin A deficiency, as an indication that hepatectomy had produced at least a mild vitamin A deficiency. However, administration of large amounts of cod liver oil in the diet of 3 hepatectomized rats did not alter the cornification in the smears.

Golden and Sevringhaus [5] and Israel, Meranze and Johnston [6] reported that normally the liver destroys the estrogen content of the blood. In the hepatectomized rats an increased amount of estrogen might have produced the constant cornification shown in the vaginal smears. The fact that the uterus had not hypertrophied (in hepatectomized rats the weight averaged 372 mg.; in normal rats, 388 mg.) indicates that estrogen was not present in an abnormally large amount.

SUMMARY

Removal of approximately 66 per cent of the liver in each of 10 rats had a stimulatory effect on spontaneous activity in 6 animals. The other 4 animals continued at the preoperative level of activity.

The partial hepatectomy had little effect on food or water intake.

It brought out a tendency to constant cornification of the cells of the vaginal epithelium as shown in vaginal smears, or a lengthening of the cycle to six days.

The partial removal of the liver had no consistent effect on the endocrine glands.

5. Golden, J. B., and Sevringhaus, E. L.: Proc. Soc. Exper. Biol. & Med. **39**:361, 1938.

6. Israel, S. L.; Meranze, D. R., and Johnston, C. G.: Am. J. M. Sc. **194**: 835, 1937.

TISSUE ANOMALIES OF PROBABLE NEURAL CREST ORIGIN IN A TWENTY MILLIMETER HUMAN EMBRYO WITH MYELOSCHISIS

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Several malformations were found in a 20 mm. human embryo. Externally, only myeloschisis in the lower half of the body was visible, but examination of serial sections revealed that this condition was associated with several irregularities of the notochord and with areas containing dystopic tissues in the sacrococcygeal region. After a short description of the anomalies found, the dystopic tissues present in the sacrococcygeal region will be discussed in detail, since they seem to represent an important stage in the genesis of certain teratoid growths.

The embryo was fixed in Bouin's fluid, embedded in paraffin and sectioned serially in transverse direction (10 microns). Azan stain was used on all sections. A graphic reconstruction of a midsagittal section was made to show the location of the structures to be described (fig. 1). Several structures lying to the sides of the midplane are also shown as projected mediad.

No malformation was noticed in the head. In the cervical region the only anomaly was a splitting of the notochord once within the first and twice within the fourth cervical vertebra. In all 3 instances the notochord was divided into two branches lying close to each other in a frontal plane (fig. 2*a*). These anomalies were restricted to a few sections of the series, after which the branches united again to form a normal notochord. No anomalies of the vertebrae accompanied these irregularities. The thoracic region was normal in appearance down to the sixth vertebra. In the following segment the anomaly of the spinal cord first appeared as an almost complete division of the organ into two symmetric lateral halves, each of them containing an extension of the central canal. This division of the spinal cord could be seen only in a short region. Two separated and closed central canals could be followed for a distance of about 0.5 mm. Then, first the right, and a few sections farther caudally the left, central canal opened on the dorsal surface of the embryo, and the spinal cord was thus transformed into a flat plate of nerve tissue with an ependymal covering on its free surface, as is characteristic for myeloschisis (fig. 1). A cranial lip of this plate overlapped the level of the divided spinal cord, and in the triangular space between this lip and the two halves of the spinal cord a ganglion was visible (fig. 3*a*), independent of the normal two rows of ganglions present throughout the length of the body. The wide open condition of the spinal cord prevailed downward to the lower lumbar region. The spinal ganglions, of which only the left row was considered

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in making the reconstruction (fig. 1), were in normal relation to the spinal cord and its nerve roots. The incomplete segmentation of this row of ganglions as indicated in this reconstruction was probably due to the fact that the narrow clefts between the segments could not be identified on cross section. The vertebral column showed marked lordosis in the region from the eighth thoracic to the second lumbar vertebra. In the lumbar region sharp kyphosis was present, due to, or resulting in, a wedgelike shape of the second and third lumbar vertebrae (fig. 1). The lower lumbar and upper sacral parts of the vertebral column again showed lordosis. The spinal cord did not follow those bends closely; only the thickness of the loose mesenchyme representing the later meninges changed considerably.

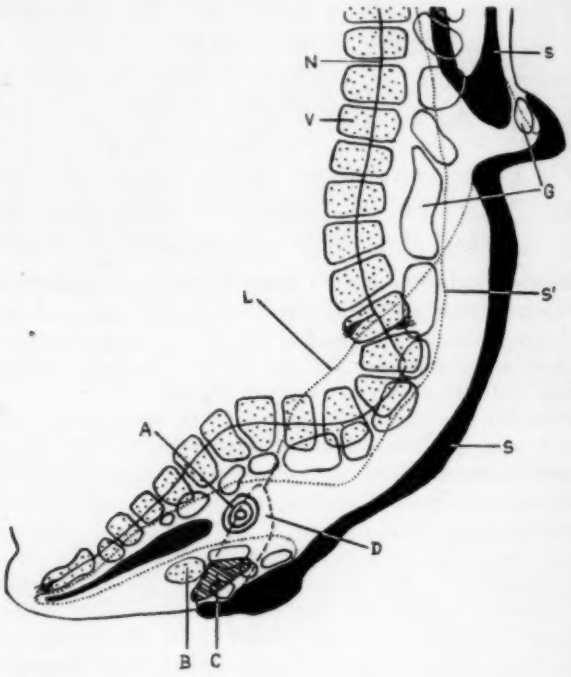

Fig. 1.—Midsagittal reconstruction of the vertebral column and spinal cord from the fifth thoracic segment downward. Several structures situated on the left side of the embryo are shown as projected on the midsagittal plane. *A, B, C,* areas of dystopic tissues designated by the same letters in the text; *D,* boundary of the area of abnormal lining of the body surface; *G,* spinal ganglions; *L,* left border of the open neural primordium; *N,* notochord; *S,* spinal cord in midsagittal section; *S'*, ventral border of the spinal cord (anterior funiculus); *V,* vertebrae.

The notochord followed the course of the vertebral column, occupying the center of the column throughout. At the level of the severest alteration of the column its configuration was abnormal again. Within the first lumbar vertebra it gave off a brushlike group of branches toward the ventral surface of the vertebra (figs. 1 and 2*b*), and in the disk between this and the following vertebra it gave off a similar group of branches dorsally. Within the second lumbar vertebra, at

the point of the sharpest bend, the notochord was absent on four sections (40 microns). Farther caudally it showed no peculiarities until it reached the end of the vertebral column.

At the level of the fifth lumbar vertebra the flat neural primordium changed its configuration in the same way as at its upper end, in the eighth thoracic segment. Here, too, it continued into two symmetric tubes with individual central canals and one "lip" lying flat on the surface. This caudad "lip," however, was so long that one could not consider it merely as the thrown-up border of the cleft spinal cord, the more so because it had several spinal ganglions apart from the rows following the closed ventral portions of the spinal cord (fig. 1). One had to assume that the neural primordium was divided at this level into a closed ventral and a flat open dorsal part. The ventral portion was subdivided into lateral halves, which united incompletely at the level of the fourth sacral vertebra. The central canals of these halves remained separated throughout. The very last division of this ventral part was completely divided again, and the thin ends lay at both sides of the last vertebral cartilage. This cartilage corresponded, under the assumption of a normal number of segments in the different divisions of the column, to the fourth coccygeal vertebra. It contained the end of the notochord, which was slightly thickened and branched. The dorsal portion of the neural primordium, after being completely separated from the ventral portion for the length of about four segments, ended at the level of the first coccygeal vertebra. At this level the aforementioned aberrant tissues were located on the left side of the body. Since I shall later discuss their probable genetic relations to the neural crest, a detailed description of the spinal ganglions in this region will be given first. As shown in figure 1, the left row of ganglions continued along the ventral portion of the central nervous system to the fifth sacral segment. (The ganglions on the right side will not be considered here.) In addition, another group of ganglions was present between the ventral and dorsal portions of the neural primordium. These ganglions were connected with the spinal cord by bundles of nerve fibers, the largest one with the ventral portion of the cord, and the three others (fig. 3 *c*) with the dorsal portion. They were connected with one another, and with similar ganglions on the right side, by bridges. One of the ganglions (figs. 1 and 2 *e* and *f*) was of particular interest because it was continuous with a cell mass which reached the body surface near the dorsal portion of the neural primordium and could not be delimited from the superficial ectoderm.

Three foci of dystopic tissue could be noticed in this region. The first of them (*A*), to be seen on craniocaudad examination of the series, was situated to the left of the ventral portion of the spinal cord at the level of the third and fourth sacral vertebrae (figs. 2 *c* and 3 *b*). It could

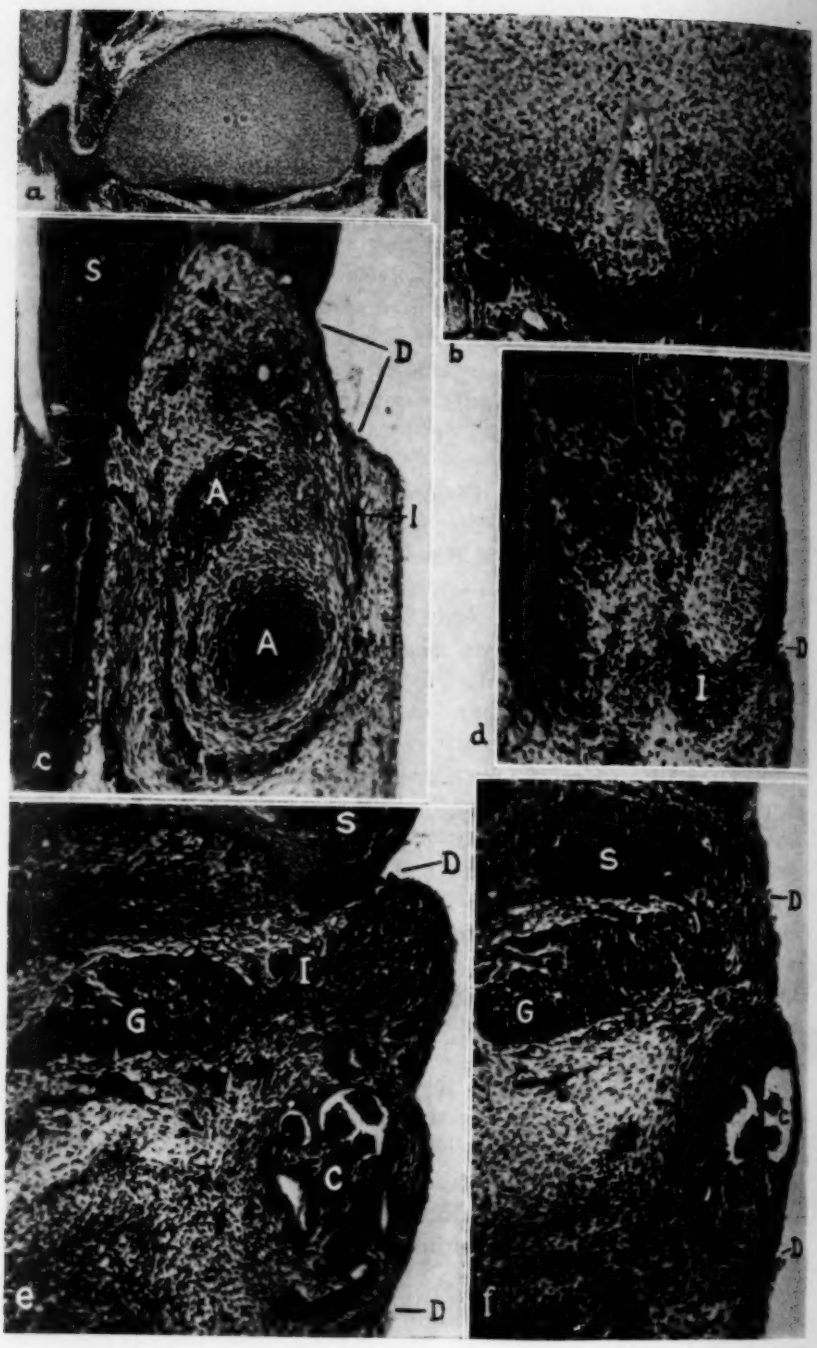

Figure 2

(See legend on opposite page)

not be successfully compared with any structure of the normal organism, since its cells were, corresponding to the age of the embryo, lowly differentiated. This focus was made up of a central mass of densely packed cells, about 120 microns in diameter, which was indistinctly bounded against a looser area (30 microns wide) identical in its structure with the mesenchyme of this embryo. This layer was incompletely surrounded by two concentric shells of denser tissue, 10 to 20 microns in thickness, separated by a 20 micron layer of mesenchyme. The two shells continued into a larger accumulation (80 microns) of the same structure on the dorsomedial side of this area (fig. 2*c*). No cytologic details could be detected which would enable one to make a comparison with normal tissues except that there was a slight resemblance of the outer shells to skeletal muscle of the same embryo.

The second area of abnormally located tissue (*B*) consisted of an irregularly shaped piece of hyaline cartilage, dorsal to the left half of the ventral portion of the spinal cord, at the level of the fifth sacral and first coccygeal vertebrae (fig. 3*c*). This cartilage lay close to several nerve bundles and was, together with them, embedded in a mass of dense mesenchyme.

A third area (*C*) contained a group of quite typical nephric glomeruli with tubules (figs. 2*e* and *f* and 3*d*), the latter being slightly tortuous and leading toward the superficial ectoderm without opening there (fig. 2*f*). These nephrons were, of course, in a location far away from the normal excretory organs and in no way whatsoever connected with them or their ducts. They could not be classified as mesonephric or metanephric.

In the region of these aberrant tissues a change was noticed in the epidermis which was of fundamental importance for the explanation of the malformations in this region. In an area labeled *D* in figure 1 the typical epidermis did not reach the border of the flat neural primordium, but changed abruptly into a quite different lining of the surface. At the first glance it appeared as if the epidermis had just been desquamated postmortally, thus exposing the subjacent mesenchyme. Careful examination revealed, however, that along this borderline, corresponding to

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EXPLANATION OF FIGURE 2

(*a*) Doubling of the notochord in a cervical vertebra. (*b*) Notochord, giving off branches, in the second lumbar vertebra. (*c*) Dystopic tissue *A* (same section as fig. 3*b*). (*d*) Stream of cells apparently moving inward from the abnormal body surface. (*e*) Dystopic tissue *C;* atypical ganglion connected to the body surface by mass of cells (same section as fig. 3*d*). (*f*) Dystopic tissue *C,* two nephric tubules converging toward the body surface at the boundary of the normal epidermis (lettering as in fig. 1). *I* indicates cells apparently moving inward from the abnormal lining of the body surface.

the left boundary of the area marked in figure 1, the epidermis changed into a layer which in many places could not be separated from the subjacent tissue. It rather appeared from the shape and position of the

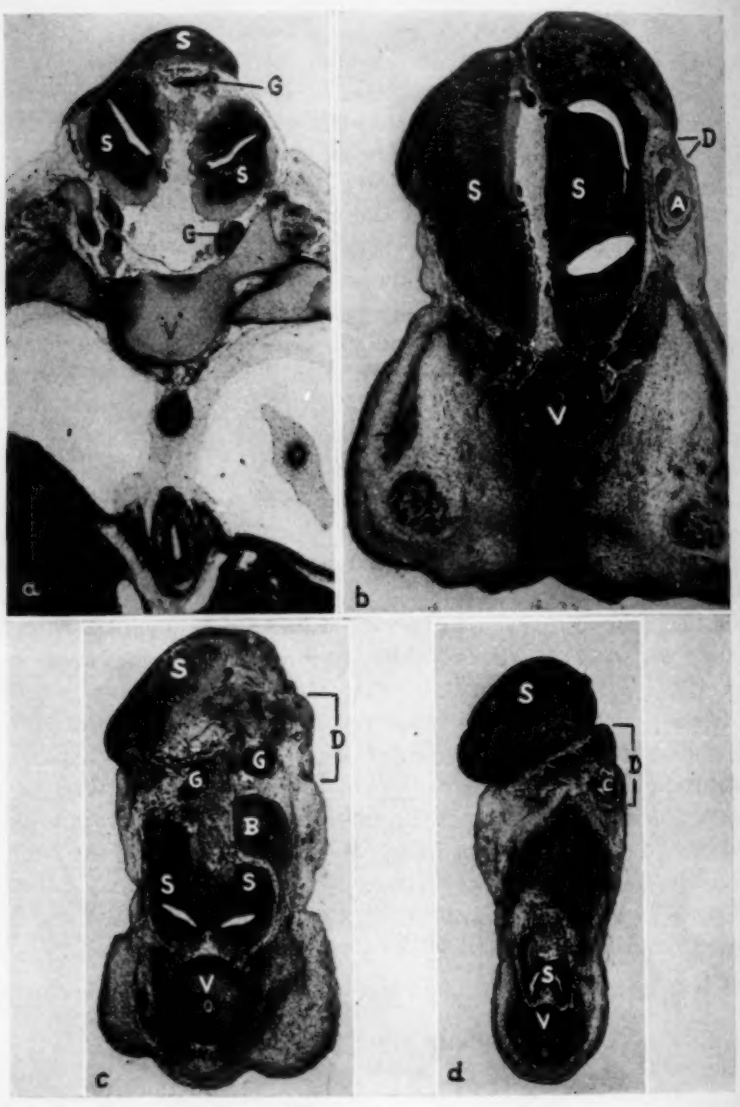

Fig. 3.—Low power photomicrographs of cross sections of the embryo: (*a*) through the cranial border of the open neural primordium; (*b, c, d*) through dystopic tissues *A, B* and *C*, respectively. Lettering as in figure 1.

cells as if streams of them were radiating toward the interior of the body from this area of the surface (fig. 2 *d*). As mentioned before, this cell mass apparently moving toward the interior of the body was continuous with one of the spinal ganglions (fig. 2 *e* and *f*) as well as with the dense mesenchyme of the first and third areas of abnormal tissues just described (fig. 2 *c* and *f*). On many sections this cell stream seemed to be particularly abundant at the border between the normal epidermis and the area of abnormal surface lining (fig. 2 *c* and *d*). Dorsally, this area was in direct contact with the maldeveloped neural primordium.

COMMENT

With the exception of the anomalies of the notochord, the condition of the vertebral column was that characteristic of myeloschisis. The irregularities of the notochord are of interest because it has been suggested that this structure exerts an important influence on the developing vertebral column (Lehmann [1]; Feller and Sternberg [2]). The finding of an interruption of the notochord at the level of the second lumbar vertebrae does not allow any conclusions; it was located at a sharp bend of the vertebral column and may very well have been a secondary tear caused by the pull at the vertex of the angle. Also unimportant from the teratologic point of view are the three splittings of the notochord in the cervical region; the halves were situated so close to one another that anomalies of the vertebrae were not necessarily to be expected even if an influence of the notochord was assumed. Of greater interest is the observation that the dorsal and ventral branches of the notochord as seen in the lumbar region were not associated with any disturbance in the structure or in the segmentation of the vertebral column. The branches reached through the vertebrae and the intervertebral disk, respectively, into the surrounding connective tissue. Anomalies must have arisen had these branches had the full power of transforming the surrounding tissue into vertebrae. However, no definite conclusions can be drawn from this single observation, either; it may gain importance in combination with future findings.

The malformation of the spinal cord apart from the most caudal segments was a typical myeloschisis. This malformation has been found in many human embryos at an early stage, as shown by Sternberg,[3] who compiled a list of many cases from the literature along with several of his own observations. There can be no doubt that this malformation develops by failure of the neural plate to form a tube. Only in caudal levels where the spinal cord does not develop from a neural plate but

1. Lehmann, F. E.: Rev. suisse de zool. **42**:405, 1935.
2. Feller, A., and Sternberg, H.: Rev. suisse de zool. **43**:701, 1936.
3. Sternberg, H.: Virchows Arch. f. path. Anat. **272**:325, 1929.

differentiates as a primarily solid cord from the trunk–tail node, the genesis of clefts of the spinal cord is not sufficiently explained. This is due to ignorance of the processes of distribution and determination of material going on in the trunk–tail node before visible differentiation. Even Holmdahl,[4] one of the best observers of trunk–tail node development, could not offer more than a far-fetched hypothesis for the explanation of myeloschisis in this region. This shows how careful one has to be in deriving conclusions regarding normal development from the study of malformations: myeloschisis in the cervical and thoracic regions, where it is an arrested stage of normal development, looks exactly like that in the lumbosacral region, where the corresponding stage does not exist in normal development. However, the peculiar differentiation of an originally solid neural primordium from the trunk–tail node explains the doubling (better, splitting) of the central canal or of the entire neural tube, as it is found almost regularly in the most caudal segments destined to degenerate soon. In the case now reported the separation into parallel parts is exceptionally marked, and the dorsal portion is separated from the two ventral ones by an unusually large mass of mesodermal tissues. This can be explained only on the basis of an extensive malarrangement of the primordia in the trunk–tail node, affecting not only the neural material but also parts of the mesoderm. The splitting of the neural tube at the cranial end of the myeloschisis has to be explained in a different manner, since this portion did not develop from the trunk–tail node. Here an abnormal folding of the neural plate into two tubes must be assumed.

The presence of spinal ganglions along all portions of the spinal cord in the sacral region is explained by the fact that in this region the neural crests do not develop independently of the neural tube, as in higher levels. According to Orts Llorca,[5] the neural crests develop by outgrowth from the dorsal portion of the neural tube caudal of the twenty-fourth pair of somites. Still further caudally, the coccygeal ganglions (thirty-first to thirty-fifth segment) arise partly or entirely from outgrowths of the ventral part of the neural tube. It is therefore quite possible that both the ventral and the dorsal portions of the neural primordium took with them the material for their own spinal ganglions when the anlage was split.

Another indication of abnormal happenings in the trunk–tail node region of this embryo was the presence of three areas containing abnormally located tissues. One of them, the cartilage *B*, may have been nothing but an attempt at formation of a skeleton, induced by the abnormally distributed nerve tissue. The two others, as well as one of the spinal

4. Holmdahl, D. E.: Morphol. Jahrb. **55**:112, 1925.

5. Orts Llorca, F.: Ztschr. f. Anat. u. Entwcklngsgesch. **102**:462, 1934.

ganglions in this region, were connected with a cell mass which was of particular interest because it seemed to radiate into the body from the superficial lining of the embryo next to the neural primordium. This relation is probably the key for the explanation of the anomalies in this area. In more craniad parts of the embryo, inward migration of cells from the boundary of the neural plate and the epidermis takes place to a considerable extent. It is known that the neural crests resulting from this process give rise not only to spinal ganglions but, probably even to a larger extent, to cells that are to be regarded as mesenchyme according to both their shape and potentialities (Raven [6]). Whereas in the segments down to the lumbar region the neural crests are well separated from the neural tube since early stages of their development, they seem to arise from the dorsal portion of the tube in the sacral region (Orts Llorca [5]). It is not well known how extensive mesenchyme formation from the neural crests is in the lower segments. However, the picture in the present case suggests so perfectly an inward migration of cells from the ectoderm next to the neural primordium and differentiation of these cells into both spinal ganglions and mesodermal structures that it seems to be the best explanation to consider this process as neural crest formation, though abnormal in extent and duration. The material thus produced had then differentiated into a ganglion, a group of nephrons (area *C*) and an evidently also mesodermal structure of unknown significance (area *A*). It cannot be determined how much of the surrounding, unspecifically differentiated mesenchyme also originated from this source. It may be easier to understand the occurrence in this region of a type of neural crest formation normally limited to levels farther craniad if one remembers that the primordium of the central nervous system, too, is found in a condition similar to a stage occurring normally only in a more craniad region, namely, that of a flat plate. Perhaps this abnormal disposition of the central nervous system is the cause of the presence of a type of neural crest formation normally not occurring at this level.

It should be mentioned in this connection that pluripotent neural crest cells were suggested as the source of abnormal growth by Masson [7] when he tried to explain the genesis of embryonal adenosarcoma of the kidney with both mesodermal and neural histologic characteristics. My case may be considered as confirming this hypothesis so far as it points more directly to the possibility of abnormal growth and differentiation originating from a neural crest.

The presence of well developed nephrons in area *C* shows an interesting aspect of tissue malformations in general and of the present case in particular, since comparatively much is known about the developmental

6. Raven, C. P.: Arch. f. Entwcklngsmechn. d. Organ. **125**:210, 1931; **129**: 179, 1933.

7. Masson, P.: Am. J. Cancer **33**:1, 1938.

physiology of the kidneys. It is a well established fact, proved by experiments of several independent investigators (Boyden [8]; Gruenwald [9]; Waddington [10]) that both mesonephros and metanephros develop only when the nephrogenic tissue is stimulated by the wolffian duct or its branch, the ureteric bud. This fact probably accounts for the great rarity of kidney tissue in dermoids and teratomas, although many of them contain a large variety of tissues. Nicholson [11] described 1 case of his own and was able to find only 2 more reliably reported in the literature. Schiller [12] described a rare type of tumor of the ovary (mesonephroma) which he considered mesonephric in origin. In all such cases one has to assume not only the presence of a tissue with nephrogenic potency in a condition allowing its activation but probably also that of a proper stimulus. Up to date observers do not know enough about the nature of such formative stimuli to be able even to guess where the stimuli might come from in such abnormally developing tissues. Since there are, however, fluent transitions between development stimulated by action of other structures and independent development, another eventuality should not be forgotten, namely, that the nephrogenic potency in those abnormal tissues may be so great that no stimulus is required for its activation.

It must be remembered that in the case presented here the nephrons developed in an abnormal location but, at least up to the time of death of the embryo, were not tumor-like. The distal ends of the tubules, normally growing toward the stimulating duct, grew toward the body surface in this case (fig. 2 *e*). It is highly doubtful, however, whether this allows the conclusion that a formative stimulus had come from the superficial ectoderm or from outside the embryo.

Dystopic kidney tissue was found in the region of the gubernaculum of the gonad by Chevassu [13] in an adult and by Meyer [14] in a 23 mm. human embryo; I found a branched epithelial tube in this region in a 21 mm. human embryo of my own collection (unpublished). In these cases, however, nephrogenic tissue can be assumed to be the source of the renal structures. The abnormally differentiated tissue was in early stages close to the wolffian duct and was possibly stimulated by it. Therefore, these cases cannot be compared with the one discussed here.

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8. Boyden, E. A.: Proc. Soc. Exper. Biol. & Med. **24**:572, 1927; Anat. Rec. **52**:325, 1932.

9. Gruenwald, P.: Arch. f. Entwcklngsmechn. d. Organ. **136**:786, 1937; Beitr. z. path. Anat. u. z. allg. Path. **100**:309, 1938; Anat. Rec. **75**:237, 1939.

10. Waddington, C. H.: J. Exper. Biol. **15**:371, 1938.

11. Nicholson, G. W.: Guy's Hosp. Rep. **84**:140, 1934.

12. Schiller, W.: Am. J. Cancer **35**:1, 1939.

13. Chevassu, M.: Bull. et mém. Soc. anat. de Paris **85**:139, 1910.

14. Meyer, R.: Virchows Arch. f. path. Anat. **204**:94, 1911.

SPECIAL CONSIDERATIONS

Apart from typical myeloschisis and unimportant anomalies of the notochord, the embryo described here showed an area containing abnormally located tissues, which illustrates the importance of neural crest material (or material formed in the same way as the neural crest) for pathologic development. The findings suggest that in this case a stream of cells originating from the ectoderm at the boundary of the neural primordium and the epidermis furnished material for at least one accessory spinal ganglion, a group of renal tubules and glomeruli, an unidentified structure and an undetermined amount of mesenchyme. The supposed origin of these cells and their differentiation into neural as well as into mesodermal structures served as the basis for a comparison with the development of the neural crest. There can be little doubt that cells derived from normal or abnormal neural crests may, because of their multiple developmental potencies, easily be the source of extraordinary and unexpected tissue malformations.

It is difficult to get a concise conception of the happenings in the region under consideration in the case presented, since so little is known about the distribution of presumptive organs in the early trunk–tail node and about the process by which this distribution is accomplished. It is well known that the sacrococcygeal region is a common location of teratoid anomalies. It may well be that in this embryo, had it survived, the area under discussion would have appeared as a teratoma. This brings up the question whether more of the anomalies classified as sacrococcygeal teratoma might have developed in the same way. One has to admit this possibility, but there is no reason to consider this as a general explanation of the genesis of teratoid malformations in that area. The presence of undifferentiated trunk–tail node material as the source of such formations will in most cases afford the better explanation, particularly if the nerve tissue present in the teratoma is more like central nervous system than like spinal ganglions.

With regard to the fact that kidney tissue normally needs a stimulus to induce its differentiation, two possibilities were considered for the explanation of the dystopic kidney tissue in the embryo in question. Either an abnormal source of stimulation must have been present in addition to the potency of kidney formation or this potency was strong enough for self differentiation.

SUMMARY

Malformations of a 20 mm. human embryo are described and discussed, consisting of myeloschisis, irregularities of the notochord and an area in the sacrococcygeal region containing several tissue malformations, among which a group of normally developed renal glomeruli and tubules is the most striking.

It is highly probable that in the area of these tissue malformations excessive neural crest formation was going on, giving rise to a ganglion, the group of nephrons, an unidentified structure and some of the surrounding mesenchyme.

This case presents an illustration of the role which cells of the neural crest, with their multiple developmental potencies, may play in abnormal development.

Renal structures which normally develop from nephrogenic tissue only when stimulated by the wolffian duct or the ureteric bud must in this case have received the stimulus from an abnormal source, or else their capacity for the formation of kidney tissue must have been abnormally strong and sufficient for self differentiation.

INTERCAPILLARY GLOMERULOSCLEROSIS

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Intercapillary glomerulosclerosis was first segregated from the other forms of nephritis by Kimmelstiel and Wilson [1] in 1936. It is a syndrome characterized clinically by mild diabetes, hypertension, retinal arteriosclerosis, albuminuria and edema, and by hyaline sclerosis of the intercapillary connective tissue of the renal glomeruli. In 1938 Anson [2] reported 6 additional cases and in 1939 Newburger and Peters [3] reported 9.[4] In a review of the last 2,000 autopsies at the Jefferson Hospital in Philadelphia I was able to find 9 cases which fulfil all the requirements previously described and a tenth which fulfils the pathologic criteria but in which the clinical data are inconclusive. The method of approach was entirely by histologic examination of consecutive file slides. The lesion is so characteristic that a total of 11 cases were separated. One of these was later discarded as doubtful. The accompanying table is a summary of the pertinent clinical and laboratory findings.

CLINICAL PICTURE

Age.—The age limits in this series are 38 and 75 years. Most of the patients whose cases are described were of middle age or beyond. One of Anson's patients was 35 years old.

Sex.—Females are somewhat more frequently affected than males. In the series reported by Newburger and Peters [3] 5 out of 7 patients were female. Of the first 9 patients whose cases are described here, 6 were female and 3 male.

Diabetes.—In the patients whose cases have been described hitherto diabetes was mild, being controlled in most instances by diet alone. In this series 5 patients (2, 3, 4, 8 and 9) required both insulin and diet, 2 (1 and 7), diet alone and 2 (5 and 6) were not known to be diabetic until the time of admission. In other words, the condition was moderately severe in 5 and mild in 4.

From the Clinical Laboratory, Jefferson Hospital.

1. Kimmelstiel, P., and Wilson, C.: Am. J. Path. **12**:83, 1936.
2. Anson, L. J.: South. M. J. **31**:1272, 1938.
3. Newburger, R. A., and Peters, J. P.: Arch. Int. Med. **64**:1253, 1939.
4. Since this article was accepted for publication, another article has been published by W. B. Porter and Harry Walker (J. A. M. A. **116**:459 [Feb. 8] 1941).

Edema.—Edema is almost a constant accompaniment. In 8 of 11 patients it was limited to the ankles and tibia. In 1 it was generalized, and in 2 it was not evident.

Hypertension.—Hypertension is usually of the benign type, varying in these patients between 140 and 220 mm. of mercury systolic and 60 and 125 diastolic. Two of the patients admitted in coma had systolic pressures of 100 and 120.

Summary of Data on Ten Cases

Case; Age, Yr.; Sex	Period Patient Was Known to be Diabetic	Edema	Blood Pressure	Retinal Condition	Urine				Blood	
					Specific Gravity	Albumin	Sugar	Casts	Sugar, Mg.	Non-protein Nitrogen, Mg.
1 74 F	3 yr.	Ankle	170/ 80	.....	1.007 to 1.018	+++	+	None	380	38
2 49 M	10 yr.	Ankle	190/110	Albuminuric retinitis	1.010 to 1.016	+++	+	Occasional	76 to 216	80 to 118
3 46 M	20 yr.	Ankles	120/ 70 Coma	.....	1.015	++	+	Occasional	486	90
4 67 F	10 yr.	Ankle	190/100	.....	1.028 to 1.032	++	+	Occasional	140 to 304	52
5 38 F	On admission	Ankles	180/ 80	.....	1.010 to 1.028	+	+	None	119 to 356	70
6 68 F	On admission	Ankles	202/ 96	Arteriolosclerosis	1.018 to 1.020	++	+	Occasional	171	63
7 75 F	Several years	Ankles	170/125	.....	1.008	++	+	Occasional	330	64
8 62 F	8 yr.	None	100/ ? Coma	Albuminuric retinitis	1.014 to 1.030	++	+++	None	330 to 438	
9 45 M	1 yr.	General	150/ 90	Arteriolosclerosis	1.010 to 1.016	++	++	Occasional	247 to 304	68 to 106
10 64 M	.....	Ankles	200/ 90	Arteriolosclerosis	1.006 to 1.014	++	..	Occasional	...	68 to 106

Eyegrounds.—Unforunately, the fundi were examined in only 5 of the 10 patients. It is to be noted, however, that all of these showed arteriolosclerosis of the vessels. In addition, 2 showed hemorrhagic extravasations and 2 both hemorrhages and exudates. Thus, in confirmation of the observation in previously described cases, retinal changes are constantly present.

LABORATORY FINDINGS

Urine.—(*a*) Albumin: The amount of albuminuria varied in different cases but it was always present. How much relation existed

between the albumin excreted and the evident edema is difficult to determine. For example, the patient in case 9, who showed generalized edema and no evidence of cardiac failure, had less albuminuria than patients who showed only slight edema about the ankles. The total blood protein and the albumin-globulin ratio would be of value in determining this relationship. These, however, were not ascertained.

(*b*) Sugar: In all cases varying amounts of sugar were shown in the urine. In some, even with slightly elevated values for blood sugar, there were only traces from time to time.

(*c*) Specific Gravity and Casts: In the short series described here, the specific gravity and casts varied so much that no special significance can be attached to them. Their presence, however, depends on the amount of associated renal damage and not on the intercapillary sclerosis as such.

Blood.—(*a*) Sugar: In the table only the high and low values for sugar are recorded. For the most part, these were not excessive, running up to 216 mg. per hundred cubic centimeters in patients whose disease was uncontrolled. The higher values are single determinations, and many of them were taken just before death. Sugar tolerance tests performed on some of the patients gave curves of the typical diabetic type.

(*b*) Nonprotein Nitrogen: In case 2 the nonprotein nitrogen was 90 to 118 mg. per hundred cubic centimeters for six and one-half months before death. This condition could be ascribed to the presence of a rather severe degree of glomerular damage. In none of the other cases was the renal involvement great enough to account for the elevated levels. Therefore, the elevation should be considered as of extrarenal origin.

OBSERVATIONS AT NECROPSY

Kidneys.—(*a*) Macroscopic Examination: Grossly, no characteristic lesions were found in the kidneys. They have hitherto been described as usually resembling those of patients with nephrosclerosis. In this series only the kidneys in cases 1 and 6 can be described as typically nephrosclerotic in appearance. The remaining 7 kidneys were greatly enlarged, weighing between 180 and 300 Gm., with an average weight of 241 Gm. The capsules of these were slightly adherent, and the cortices were finely granular. Generally, the latter were relatively thickened, and the corticomedullary demarcations were slightly obscured or normal. Some showed a slight degree of gray radial streaking. The arterioles were not prominent. The peripelvic fat tissue was not increased.

(*b*) Microscopic Examination: Three stains were used, namely, ordinary hematoxylin and eosin, Kimmelstiel's [1] basement membrane stain and the congo red stain for amyloid. The latter was negative in all cases.

In the glomeruli a hyaline thickening of the intercapillary connective tissue is the characteristic lesion. Most of the glomeruli show some

Fig. 1.—*A*, patent peripheral capillaries with discrete intercapillary basement membrane. *B*, large masses of hyaline material in the intercapillary connective tissue. *C*, connection of intercapillary hyaline material with that in the wall of an afferent vessel. (Tissue fixed in Zenker's solution; Kimmelstiel's basement membrane stain; blue filter.)

changes. With the basement membrane stain, varying degrees of involvement can be found. Either the entire glomerulus (fig. 1) or a portion of a glomerulus (fig. 2) is involved. The initial changes appear to start in the center and work toward the periphery. There is a gradual thickening and hyaline sclerosis of the connective tissue, with increasing crowding together and peripheral pushing of the capillaries.

Ultimately, large globules of this hyaline material are formed within the glomerulus, sometimes occupying most of the tuft. With the ordinary hematoxylin and eosin stain this material appears as bright pink to red, and with Kimmelstiel's basement membrane stain, as blue to purple. At the periphery [1] of the glomerular tuft the basement membrane emerges from these hyaline masses as a fairly broad band. It

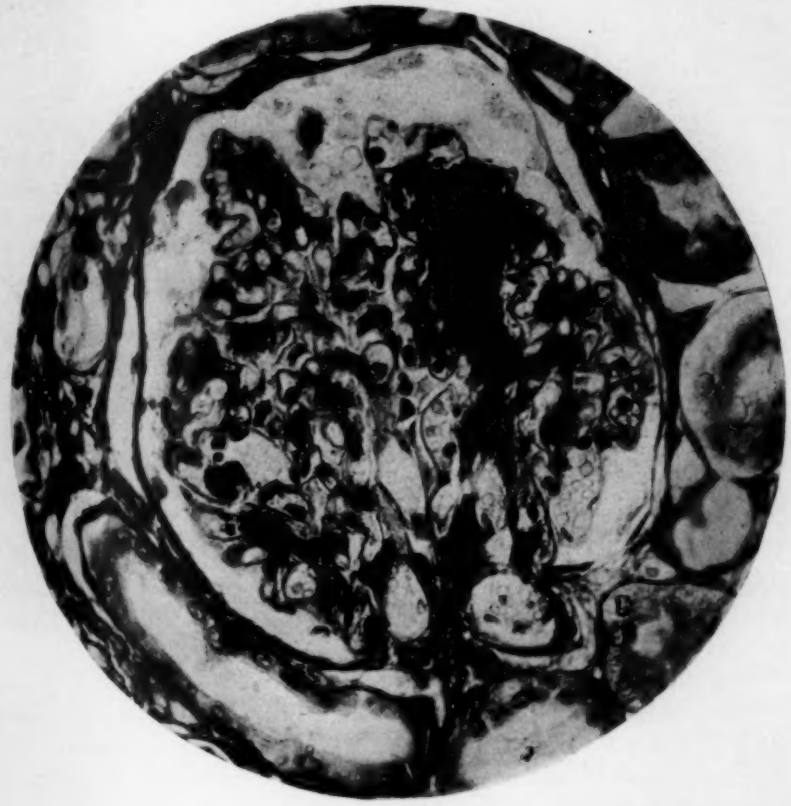


Fig. 2.—A predominating segmental distribution of intercapillary hyaline material is shown. Note the patent peripheral capillaries and discrete intercapillary basement membrane. (Tissue fixed in Zenker's solution; Kimmelstiel's basement membrane stain; no filter.)

rapidly attenuates, however, until it exists as a fine thread coursing between the capillaries. In this region it is never blurred, wavy or split. The latter observation is of primary importance in distinguishing this, a degenerative lesion, from one of inflammatory origin. In cases in which the conditions are fairly advanced, the capillaries of the entire central portion may be completely obliterated with this hyaline material. Even in these, however, the peripheral capillaries not only are patent

but sometimes appear to be somewhat dilated. Ultimately the capillaries are entirely obliterated, leaving the glomerulus as a solid mass of fibrous tissue and hyalin. In kidneys which show marked arteriolosclerosis there is often direct continuation between the hyaline material in the glomerulus and that in the wall of the afferent artery (fig. 1).

Bowman's capsule shows some thickening of the basement membrane, which, with routine staining, is represented first as a narrow pink hyaline band. In the more advanced lesions this appears to be replaced by a broader, somewhat trabeculated meshwork of much fainter-staining pink material. That it is deposited between the capsular basement membrane and its epithelial cells, as described by Kimmelstiel and Wilson,[1] cannot be determined. It appears rather that the basement membrane itself is responsible for the change, since it can be seen to fade gradually into or emerge from this hyaline or "fibrous" substance. The presence of lipoids and fats, as originally described, cannot be seen in the ordinary hematoxylin and eosin sections. Material for fat stains was not available.

The capsular space is not affected in the earlier stages. As the lesion progresses and the capillaries of the tufts are pushed aside, the space becomes smaller and smaller until ultimately it is entirely obliterated. In many intermediate stages it is interrupted by adhesions between the tuft and the capsule.

The arterioles in practically all of the cases show some degree of sclerosis, exhibiting the usual deposition of hyalin.

In the tubules, if fat and lipids are present, the amount is not sufficiently great to be seen in hematoxylin and eosin sections. Glycogen droplets, which are sometimes observed in cases in which the disease process is uncontrolled, are not found in any of the sections.

The interstitial connective tissue reveals no specific lesions.

Of associated renal conditions, benign nephrosclerosis is an accompanying lesion in most of the cases. There are some cases, however, especially those in which younger patients are concerned, in which no other pathologic changes are demonstrable.

Pancreas.—There are, as a rule, no gross changes in the pancreas. Microscopically, in some cases a varying degree of lipomatosis and interstitial fibrosis are seen, but no demonstrable changes in the islets of Langerhans.

Heart.—There is usually moderate hypertrophy of the left ventricle, as seen in benign hypertension. There are likewise varying degrees of coronary arteriosclerosis and pseudoscarring.

Arteries.—Generalized arteriosclerosis is usually very marked. In cases 1, 2, 4 and 8 one lower extremity was amputated because of gangrene.

Cause of Death.—Death in these cases was usually due to cardiac failure, diabetes with its various complications, or renal failure. Each cause was noted with approximately equal frequency.

DIFFERENTIAL DIAGNOSIS

From the pathologic standpoint one must distinguish intercapillary glomerulosclerosis from intracapillary glomerulonephritis of Fahr and amyloid disease. The latter affords no difficulty, for there is usually evidence of chronic infection elsewhere, notably tuberculosis or osteomyelitis, and accompanying involvement of the liver and spleen. Various amyloid stains are negative in intercapillary glomerulosclerosis. For a complete differentiation from intracapillary glomerulonephritis, the reader is referred to the original article of Kimmelstiel and Wilson.[1] Only two of the outstanding features of intracapillary glomerulonephritis will be mentioned here. In the acute stage there is present an inflammatory exudate which makes recognition easy. In the chronic stages it is sometimes impossible to distinguish between the two. In intracapillary glomerulonephritis, however, there are blurring and reduplication of the glomerular basement membrane, whereas in intercapillary glomerulosclerosis the membrane remains discrete and single.

SUMMARY

From the evidence at hand it seems to be quite conclusive that intercapillary glomerulosclerosis can be separated from the other forms of nephritis as a definite syndrome. This syndrome is present in only a minority of patients with diabetes but, when present, it consists of diabetes, hypertension, retinal arteriosclerosis albuminuria and edema. Pathologically, the kidneys exhibit characteristic hyalinization of the intercapillary connective tissue of the glomeruli. Since the morphologic criteria for the diagnosis of diabetes are so meager, it is important to note that this hyaline sclerosis affords another means of identification in a certain number of cases.

Case Reports

CARCINOID IN STOMACH TISSUE WITHIN AN OVARIAN DERMOID

JACQUES LESTER GABRILOVE, M.D., NEW YORK

A 29 year old white woman died of malignant nephrosclerosis. At autopsy, immediately after the peritoneal cavity was opened, an ovarian dermoid cyst became visible, measuring 11 by 9 by 8 cm. From its outer surface, an intestine-like coil, 10 cm. long, protruded. The tip of this coil was fixed to the cyst by dense adhesions. The coil, as well as the other many locules of the dermoid cyst, contained hairs and tallow. The inside of the tip of the coil had a velvety, somewhat villous-appearing surface. The inside in the proximal portion was suggestive of gastric mucosa with distinct areolas. The remainder of the ovarian dermoid gave the usual picture. There were cartilaginous and bony portions.

Microscopically, the usual variegated pictures of a dermoid cyst were present. In the wall of the coil, the lining, corresponding to the gross aspect, gave the picture of intestinal mucosa and of gastric mucosa. In the gastric mucosa, near the edge, a carcinoid was found. It did not form one continuous mass but was composed of more or less scattered epithelial heaps. The largest continuous portion had a diameter of 3 mm. Some of the epithelial masses at the periphery bore a certain resemblance to aberrant pancreatic tissue. The material could not be studied in serial sections; therefore the size of the tumor remains unknown.

The tissue in which the carcinoid was situated was not normal. Definite parietal cells and Brunners glands proved that one was dealing with stomach tissue. However, the different layers of the stomach wall could not be seen distinctly. The muscularis mucosae and the muscle coat appeared fused, and no submucosa could be made out.

These findings bring the following questions to mind: 1. What is the frequency of neoplasms arising in ovarian dermoids? 2. What is the frequency of stomach tissue in dermoid cysts? 3. What is the incidence of carcinoids in stomach tissue?

A neoplasm arising in a dermoid cyst is uncommon. The most frequently encountered type is epidermoid carcinoma; about 60 cases have been reported in the literature.

Miller,[1] although referring to several cases in which stomach tissue was found in a dermoid cyst, did not mention any observation in which the stomach tissue was identified with the naked eye.

Ewing[2] also mentioned instances of stomach tissue being found on microscopic examination of dermoid cysts.

From the Department of Pathology, Beth Israel Hospital.

1. Miller, J.: Weibliche Geschlechtsorgane, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1937, vol. 7, pt. 3.

2. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940.

Plaut,[3] in a recent review of the literature concerning carcinoid of the stomach, discussed 10 cases, including 1 case of his own. To these should be added 1 case observed by Bailey [4] and 2 cases observed by Porter and Whelan,[5] whose report appeared at the same time as Plaut's.

Bailey's case was that of a 66 year old woman who had died of erysipelas. The carcinoid, 13 mm. in diameter, was located on the lesser curvature of the stomach, 4 cm. below the cardia.

Porter and Whelan do not give either gross or microscopic details of their cases.

Only 2 instances of a carcinoid arising in an ovarian dermoid could be found recorded in the literature.[6] The first case was that of a 60 year old woman operated on for a dermoid cyst of the ovary. The carcinoid was situated in smooth muscle, which, in the opinion of the authors, represented intestine. The second case was that of a 48 year old woman with a dermoid cyst. The carcinoid was found infiltrating the smooth muscle of intestine within the wall of the dermoid cyst.

Little can be added in the way of comment. My patient was the second youngest of the patients in whose cases a carcinoid was reported found in stomach tissue. The combination of three rarities, a carcinoid in an ovarian dermoid, grossly identifiable stomach tissue in a dermoid and a carcinoid in stomach tissue, defies any attempt at interpretation.

SUMMARY

A case is reported of a carcinoid arising in stomach tissue which formed part of an ovarian dermoid. This is the third case of a carcinoid in an ovarian dermoid and the fourteenth case of a carcinoid in stomach tissue.

3. Plaut, A.: Arch. Path. **28**:712, 1939.

4. Bailey, O. T.: Arch. Path. **18**:843, 1934.

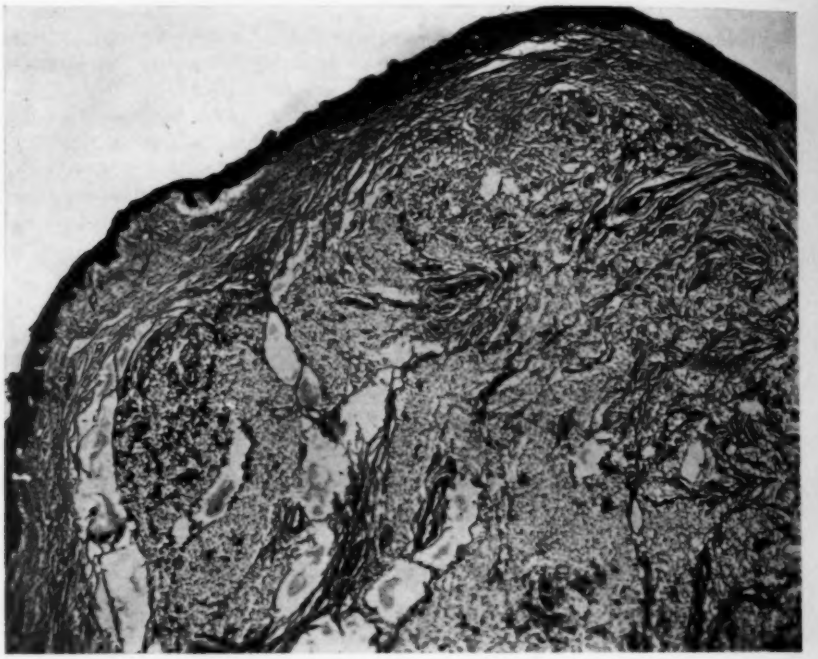
5. Porter, J. E., and Whelan, C. S.: Am. J. Cancer **36**:343, 1939.

6. Stewart, M. J.; Willis, R. A., and de Saram, G. S. W.: J. Path. & Bact. **49**:207, 1939.

LIPOMA OF THE TONGUE

BÉLA HALPERT, M.D., NEW ORLEANS

The normal tongue contains adipose tissue, yet lipoma of the tongue is rare. Less than 50 such tumors are on record, 35 of which were listed by Colombo,[1] in 1932. The largest lipoma of the tongue was reported by Ferris Smith,[2] in 1937, in a 45 year old white woman; it was 11 by 9 by 7 cm. and weighed 320 Gm. Two large ones have been reported



Lipoma of tongue from a 55 year old Negro woman. The growth is composed of various-sized lobules of adipose tissue with loose connective tissue septums containing blood vessels.

since. The first, observed by Paul,[3] occurred in a 43 year old male Singhalese; it was about the size of a tangerine and weighed 6 ounces

From the departments of pathology and bacteriology of the Charity Hospital of Louisiana at New Orleans and the Louisiana State University School of Medicine.

1. Colombo, A.: Tumori **6**:233, 1932.
2. Smith, F.: J. A. M. A. **108**:522, 1937.
3. Paul, M.: Lancet **2**:997, 1938.

(170 Gm.). The second, recorded by Mudaliar,[4] occurred in a 30 year old woman and was the size of an orange.

In the reported cases the growth has occurred almost twice as frequently in men as in women.[2] Information on the race incidence is not available. It seems likely, however, that none of the reported neoplasms were seen in Negroes.

REPORT OF A CASE

A 55 year old Negro domestic servant was admitted to the Charity Hospital of Louisiana, May 28, 1940, in order to have a mass removed from her tongue. The mass had been present for ten years and had gradually reached its present size. It was not painful, did not bleed, and bothered her only by its presence. The past history was irrelevant. The only positive finding was a spherical mass, 1 cm. in diameter, pedunculated, which protruded from the left border of the tongue about 3 cm. from the tip. It was covered with intact mucosa and was moderately firm. The mass was excised June 3 (by Dr. R. P. Hays), and the patient was discharged five days later.

The specimen consisted of a wedge-shaped portion of tongue, 1 by 1 by 0.7 cm. Longitudinal section through the center showed slight bulging of the cut surfaces, which were soft and composed of lobules of pale yellow adipose tissue. Routine microscopic preparations, stained with hematoxylin and eosin, disclosed various-sized lobules of adipose tissue cells with loose connective tissue septums containing blood vessels (fig. 1). A delicate connective tissue capsule surrounded the growth and blended with both the intermuscular connective tissue and the tunica propria of the mucosa. In the stratified squamous epithelium covering the surface, intercellular bridges were clearly discernible, and keratinization was marked toward the surface.

SUMMARY

A lipoma of the tongue in a 55 year old Negro woman is reported. This apparently is the first such growth in a Negro to be recorded.

4. Mudaliar, K. S. A.: Antiseptic **36**:1127, 1939.

MYOBLASTOMA OF THE THORACIC WALL

DAVID M. GRAYZEL, M.D., PH.D., AND H. HAROLD FRIEDMAN, M.D., BROOKLYN

In 1926 Abrikossoff [1] called attention to a tumor arising from embryonal muscle cells in close relationship to striated muscle. Believing that these cells resembled the primordial muscle elements found in the myotomes of embryos, he called the tumor *Myoblastenmyome*. Myoblastoma of striated muscle is exceedingly rare. Only 50 cases had been reported up to 1934, according to Klemperer,[2] who made a comprehensive survey of the cases reported up to that time. Since then other cases have been described in the literature. In 1937 Gray and Gruenfeld [3] had collected 77 instances, including 5 of their own. The lesions have been found in various locations, with a predilection for the upper parts of the digestive and respiratory tracts; 34 were found in the tongue, 2 in the lip, 4 in the maxilla, 2 in the mandible, 8 in the vocal cord, 1 in the esophagus, 6 in the mammae, 9 in the skin, 3 in the subcutis of the sacral region and 8 in muscles of the extremities. In 1939 Kramer [4] reported a case of myoblastoma of the bronchus, making the total number of cases of myoblastoma reported to date 78. No such tumor has yet been described as occurring in the wall of the chest except for a few noted in the mammae. The case to be presented is the first of a myoblastoma occurring in the thoracic wall. Since the subject has been so adequately reviewed by Klemperer and by Gray and Gruenfeld, it was felt unnecessary to review it again.

REPORT OF A CASE

In December 1939 a woman 45 years old began to complain of a painful lump in the lower portion of the right axillary space. This growth seemed to be attached to the underlying rib. The roentgenologist's report was indefinite as to the possible bony origin of the growth. The tumor did not increase in size but continued to be painful. Excision was recommended and performed on June 15, 1940 by Dr. M. J. Rader. A stony-hard globular mass about the size of a hazelnut was found in the deep subcutaneous tissue overlying the fascia of the external intercostal muscle. The tumor and a moderate amount of adherent fat were completely dissected away. The postoperative course was uneventful. No recurrence has taken place.

Pathologic Report.—Grossly, the specimen was a piece of firm pink-yellow tissue, measuring 2.7 by 2.5 by 1.5 cm. The external surface was covered by lobules of adipose tissue. In the cut surfaces there was a well circumscribed nodule, 1.5 cm. in diameter, which was composed of strands of gray fibers enclosing pale amber tissue.

From the Department of Laboratories of the Jewish Hospital.

1. Abrikossoff, A.: Virchows Arch. f. path. Anat. **260**:215, 1926; **280**:723, 1931.

2. Klemperer, P.: Am. J. Cancer **20**:324, 1934.

3. Gray, S. H., and Gruenfeld, G. E.: Am. J. Cancer **30**:699, 1937.

4. Kramer, R.: Ann. Otol., Rhin. & Laryng. **48**:1083, 1939.

Microscopically, the tumor consisted of nests and cords of large irregular polyhedral cells. The nuclei were round or oval and were situated centrally or peripherally. They stained heavily and sometimes contained nucleoli. Occasional cells were giant sized and contained several nuclei. The cytoplasm was coarsely granular and basophilic. The granules were irregularly arranged, being closely packed in some cells and more loosely arranged in others. Their arrangement in parallel rows in some instances suggested the cross striations of striped muscle fibers. In places the cells were arranged in irregular syncytial masses and were separated by delicate bands of fine connective tissue fibrils with slight infiltrations

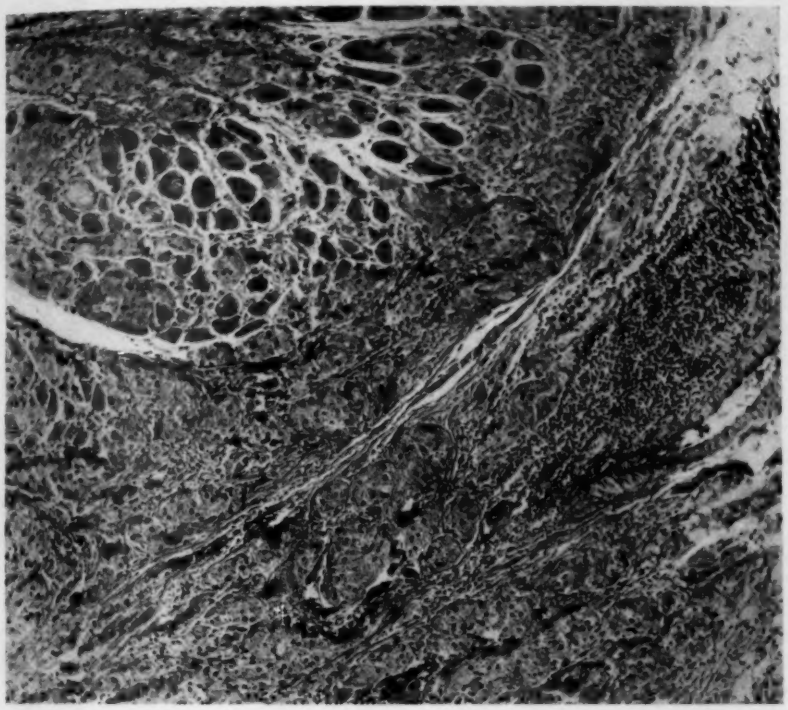


Fig. 1.—Photomicrograph showing tumor cells and well preserved striped muscle cells. Hematoxylin and eosin; × 80.

of small round cells and large mononuclear cells. Some of the tumor cells appeared to merge with groups of well preserved striped muscle fibers. With scarlet red stains, the cells were seen to contain no fat.

The diagnosis was myoblastoma of the wall of the chest.

COMMENT

Under the term "myoblastoma" have been included tumors composed of large irregular polygonal cells containing deep staining nuclei and coarsely granular cytoplam. Myoblastoma resembles xanthoma except that no fat can be demonstrated in it with special staining methods. When it occurs in close relationship to striated muscle, where transitional

states can often be seen between the tumor cells and the muscle fibers, the myogenous nature can be readily recognized. When, on the other hand, it is found in a site where no striated muscle is present, one has to postulate a dysontogenetic origin for its cells. This implies that during the early stages of development primordial muscle cells of the myotomes become included within cell complexes that migrate to form these other structures. Gray and Gruenfeld, with some justification,

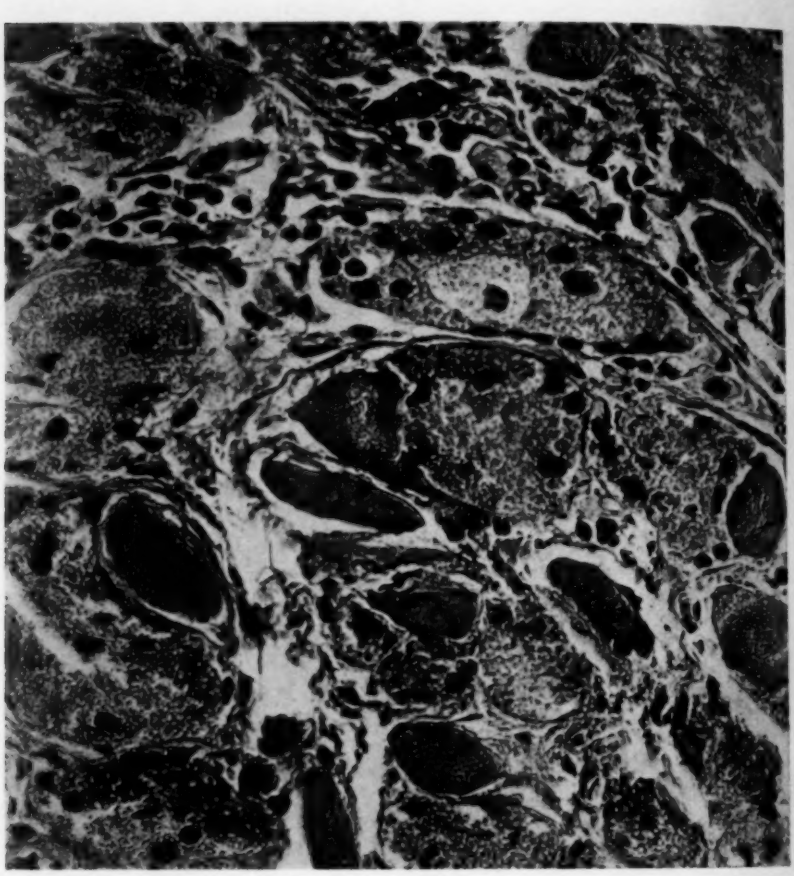


Fig. 2.—A higher magnification of a portion of the tumor tissue shown in figure 1. Hematoxylin and eosin; × 400.

question the myogenous derivation of myoblastoma in such a site, since the only reason for including it in this group is that there is close similarity of the histologic pictures.

The exact nature of the tumor cells is still in doubt. Some have considered myoblastoma as an example of imperfect rhabdomyoma, but in the present tumor the histologic features of that tumor are lacking. Others have felt that a granular degeneration due to trauma of the muscle might be implicated as a possible etiologic factor. This, how-

ever, could apply only to the tumor arising in close proximity to striated muscle. Myoblastoma, moreover, is relatively slow growing. The cells are fairly uniform, and the nuclei do not show the marked variability and staining reactions usually associated with malignant tumors.

Myoblastoma occurs most frequently in the third to fifth decades. It is a benign, small, slow growing tumor which does not tend to recur after complete removal. Only 1 case was reported in which there was a recurrence of the tumor, with metastases. However, there is a question whether or not this tumor was initially rhabdomyosarcoma.

The tumor described in this paper meets all the criteria of myoblastoma mentioned in the literature. Moreover, it arose in close relationship to striated muscle and in places showed transition states between tumor cells and striped muscle fibers.

General Reviews

RELATION OF THE CHEMICAL COMPOSITION OF LIPIDS TO CHARACTERISTIC TISSUE LESIONS

EDWIN F. HIRSCH, M.D.
CHICAGO

The lipids, a large heterogeneous group of organic substances of the body and foods, include the fats, oils, waxes, phospholipids and sterols. The metabolism of the lipids of the body proceeds usually to completion, so that no or little residue of the lipid material remains. In systemic disorders, however, and locally in pathologic tissues or wherever lipids by some means are introduced into structures of the body, the usual disposal does not occur, and tissue reactions develop about the accumulated lipid substances.

Probably the simplest of these lesions occurs in the subcutaneous and other fat tissues of the body. Abrikossoff,[1] in 1926, reported the spontaneous appearance of painful nodes in the subcutaneous fat of patients with spotted or recurrent fever, within a few weeks to a year after the onset of the illness. In the evolution of these lesions the initial stage is focal necrosis of the fat without hemorrhage or inflammation. Exudates of lymphocytes, leukocytes and polyblasts appear about the focus. The cell membranes of the fat cells disintegrate and droplets of fat are released into the tissues. These become encapsulated in the granulation tissues. Giant cells form along the margins of the lipid substances, and in old lesions oval or round crevices in the scar tissues contain fat material or serous fluids. Calcium deposits later may solidify the entire lesion. Abrikossoff viewed the lesion as a focal necrosis of the fat caused through injury by a toxin or a circulatory disturbance. The lipids freed or hydrolyzed stimulate an inflammatory reaction which is to some extent foreign body in nature. Makai [2] introduced the descriptive term "subcutaneous lipogranulomatosis" for these lesions. He expressed the belief that trauma, toxic agents, circulatory disturbances and injections were causal agents. He suggested the remote possibility of a hormonal or a constitutional factor. Makai agreed with Abrikossoff as regards the sequential evolution of the lesions, namely, necrosis of fat tissues with subsequent transformation of neutral fats into fatty acids or

From the Henry Baird Favill Laboratory of St. Luke's Hospital and the Department of Pathology of the University of Chicago.

1. Abrikossoff, A.: Centralbl. f. allg. Path. u. path. Anat. **38**:542, 1926.
2. Makai, E.: Klin. Wchnschr. **7**:2343, 1928.

soaps and an inflammatory reaction of the surrounding tissues. According to Goldzieher,[3] the lesions occur in fat tissues of any part of the body, specifically the mammary gland, subcutaneous fat, lipomas, mesentery, retroperitoneum and bone marrow. All writers agree that the lipids released through necrosis of fat tissues stimulate the granulation tissues characteristic of the lesion.

Eckstein [4] reported the average lipid content of hydrolyzed subcutaneous human fat as follows: nonsaponifiable material 0.37 per cent, unsaturated fatty acids 63.6 per cent and saturated fatty acids 26.6 per cent. Of the unsaturated fatty acids, oleic acid was present in large amounts, but others with two, three and four double bonds were demonstrated. Of these, linoleic acid predominated. Cholesterol in the amount of 0.24 per cent was found. These analyses indicate the chemical nature of the primary lipids concerned with the tissue reactions following necrosis of subcutaneous fat.

Information concerning the effects of diet on the composition of fat in the depots of the body has been obtained from studies in lower animals. Ellis and Isbell [5] examined the effect of food fat on the composition of body fat in swine. They fed diets with a low, a moderate and a high fat content. The fatty acids identified in all fat tissues were oleic, linoleic, arachidonic, myristic, palmitic and stearic. Soybeans in the food caused deposition of small quantities of linoleic acid; peanuts, arachidic acid. The oils in these two dietary substances had a pronounced effect on the composition of the lard, though a greater likeness was noted between the peanut oil and the "peanut lard" than between the soybean oil and the "soybean lard." Fat formed on a diet containing less than 1 per cent fat was very hard, and the glycerides of oleic, palmitic and stearic acids composed over 97 per cent of the fat. Longenecker [6] reported that the depot fat laid down after fasting by rats fed a diet high in corn oil was almost identical in fatty acid composition with the oil, and its composition was modified but slightly with inanition. After fasting, an equicaloric ration containing sucrose instead of corn oil caused a marked increase of the palmitic and hexadecenoic acids. The results of these experiments indicate possible variations in the composition of human fat with diet. The composition of the subcutaneous fat is modified also with age and by wasting diseases. Stolfi [7] reported that adult human adipose tissues contain more oleic acid than those of children. He stated that the liquid fatty acid content in normal persons was 68.3 per cent, in hosts with benign tumors 68.0 per cent,

3. Goldzieher, M.: Arch. Surg. **23**:690, 1931.
4. Eckstein, H. C.: J. Biol. Chem. **64**:797, 1925.
5. Ellis, N. R., and Isbell, H. S.: J. Biol. Chem. **69**:239, 1926.
6. Longenecker, H. E.: J. Biol. Chem. **129**:13, 1939.
7. Stolfi, G.: Boll. Soc. ital. di biol. sper. **9**:108, 1935; abstracted, Chem. Abstr. **29**:4781, 1935.

in patients with malignant tumors 71.7 per cent and in those with cancerous cachexia 77.7 per cent. The cholesterol content in these was, respectively, 0.38, 0.43, 0.86 and 0.75 per cent.

The reactions aroused by the lipids released into the tissues are caused, apparently, by hydrolyzed and unhydrolyzed fat. The effect of the latter is comparable to that of an inert oil, like liquid petrolatum,[8] unless some internal chemical change occurs. The hydrolysis of fats introduces a chemical factor. So far as is known, glycerol liberated by the hydrolysis of fats has no appreciable effect on the tissues. It dissolves readily and diffuses rapidly in the fluids of the body. The chemical effects of the fatty acids and of their compounds in the tissues are much more complex. Some writers have expressed the opinion that other substances, such as cholesterol and phosphatides, are important causes of the tissue reactions. Wail[9] observed a gradual increase of cholesterol and phosphatide compounds in human fat injected subcutaneously into rabbits. According to the view shared by Makai, von Quierke and Askanazy,[10] the fat of the necrotic tissues is split rapidly into fatty acids by the tissue lipases, and the fatty acids are the irritating substances that stimulate the lipophage reaction. Ansart and Got expressed the belief that the unsplit neutral fat provokes the inflammation.

Klotz,[11] in studies of tissue calcification, embedded capsules containing palmitic acid and stearic acid and their sodium soaps in the peritoneums of rabbits. After several days, the calcium content of the materials within the capsules was greater than that of the blood and lymph. Langmuir and Schaefer[12] found that monomolecular films of stearic acid floating on water containing calcium or barium salts were converted completely or partly into the corresponding soaps of the fatty acids. The extent of this reaction depended on the hydrogen ion concentration of the aqueous medium. These observations demonstrated the transfer of base ions dissolved in an aqueous solution to fatty acids across a water-oil interphase. With the establishment of equilibrium in such water-oil systems, hydrogen ions migrate from the oil into the aqueous solution. This is demonstrated readily by shaking an alkaline solution, such as calcium hydroxide, containing an indicator, with a small quantity of liquid fatty acid. The color of the indicator rapidly shifts into the acid range. According to Hartsuch,[13] when an

8. This review does not include tissue reactions produced by preparations of liquid petrolatum.

9. Wail, S. S.: Virchows Arch. f. path. Anat. **245**:219, 1923.

10. Cited by Ansart, M. B., and Got, J. d'H.: Arch. f. klin. Chir. **172**:724, 1933.

11. Klotz, O.: J. Exper. Med. **7**:633, 1905; **8**:322, 1906.

12. Langmuir, I., and Schaefer, V. J.: J. Am. Chem. Soc. **58**:284, 1936.

13. Hartsuch, P. J.: Arch. Path. **25**:17, 1938.

excess of oleic acid is in contact with an aqueous solution of sodium or potassium hydroxide, the soap formed is distributed between the aqueous and the oil phases. With calcium hydroxide and an excess of oleic acid, the relations differ. Because the calcium oleate formed is almost insoluble in water and is soluble readily in oleic acid, the calcium oleate at equilibrium is found only in the oil phase. Hartsuch investigated the exchange of ions between dilute aqueous solutions of magnesium acid phosphate ($MgHPo_4$) and oleic acid in relation to the p_H of the aqueous medium. Only a slight exchange of ions occurred at p_H 5.7, but as the acidity decreased, a correspondingly larger percentage of magnesium was transferred from the aqueous solution to form magnesium oleate, dissolved in the excess of oleic acid present. Large amounts were transferred when the aqueous medium was alkaline. H ions at the same time passed from the oil phase into the aqueous solution, lowering the p_H of the water medium.

The effects of the fatty acids in the tissues, then, may be analyzed on the basis of: (1) the degree of acidity produced, (2) the soap formed and (3) the chemical structure of the fatty acid. The acidity which fatty acids when liberated by hydrolysis may cause in tissues of the body is not known. Hartsuch's investigation of the transfer of magnesium from an aqueous solution to oleic acid demonstrated that very little exchange of ions occurred when the p_H of the aqueous solution was approximately 5.7. This p_H probably is the maximum that would develop in an aqueous medium exposed to oleic acid. Comparable information for other fatty acids is not available, but probably would not differ appreciably. Intravenous or subcutaneous injections of oleic acid cause marked necrosis of the tissues (lungs, kidneys) [14] where the lipid lodges. The tissue response is mainly a marked growth of collagenous connective tissue.

Pinkerton [15] expressed the opinion that the necrosis of lung tissues about fats and oils is due to the free fatty acids. Among the lipids investigated, lard and chaulmoogra oil were the two lipids which produced necrosis in lung tissues. They had by far the highest free fatty acid content. By assuming that the tissue reaction to a fat or an oil depends on the content of free fatty acid and on the speed of liberation of the fatty acid by hydrolysis, Pinkerton derived what he believed to be a satisfactory explanation for his observations in the lung tissues of rabbits. The lack of reaction to the neutral vegetable oils was due, he thought, to the absence of hydrolyzing enzymes. Cod liver oil, in contrast, was rapidly hydrolyzed, and at first there was no necrosis; later, it was marked.

14. (*a*) Hirsch, E. F.: Arch. Path. **21**:765, 1936. (*b*) Hagerty, C. S.: ibid. **25**:24, 1938.

15. Pinkerton, H.: Arch. Path. **5**:380, 1928.

Sabin, Doan and Forkner [16] demonstrated that the substances in tubercle bacilli responsible for the typical tuberculous tissues are limited to the lipid fractions. Hydrolysis of a fraction designated phospholipid A_3 yielded a liquid saturated fatty acid which, in contrast to other phosphatide subfractions, stimulated extensive formation of tuberculous tissues, such as aggregates of epithelioid cells and some epithelioid giant cells. The active principle for the production of typical tuberculous tissues, they concluded, is carried by this fatty acid. These two substances, the phosphatide and its saturated fatty acid, are far more important in the production of tuberculous tissues than the other principal lipid fractions, the waxes and glycerides and the products of their hydrolysis. The nonspecific lipid fractions, palmitic acid, glycerophosphoric acid and stearic acid, produced nonspecific irritative reactions, primarily clasmatocytes, monocytes and epithelioid cells.

Fatty acids solid at body temperature, such as stearic, when separated from a liquid fat in the tissues, cause the tissue stimulus of a solid substance and the formation of foreign body giant cells.[14a] A factor in this is supersaturation, probably by removal of the solvent.

The effects of soaps and esters of fatty acids also have been investigated. Hirsch [14a] observed that human fat containing low concentrations of free oleic and stearic acids neutralized with calcium hydroxide stimulated a moderate fibroblastic tissue response. After neutralization with strontium or barium hydroxide, this mixture stimulated a marked reaction of fibroblastic tissues with epithelioid and giant cells. The insolubility of the strontium and barium soaps contributed apparently to the structure of the lesions and to the formation of giant cells. Hass [17] noted that the natural and the synthetic glycerides of fatty acids containing long chains of carbon are not hydrolyzed in the subcutaneous tissues at an appreciable rate, and those with short chains disappear slowly. He observed that methyl esters of long chain saturated and unsaturated fatty acids are rapidly hydrolyzed, the ethyl esters of representative long chain acids are slowly hydrolyzed, and the N-butyl esters are not split to an extent readily detectable by the methods employed. Isoamyl and secondary octyl esters of stearic acid persist unchanged in the subcutaneous tissues, whereas tetrahydrofurfuryl palmitate is hydrolyzed rapidly at a rate comparable to the methyl palmitate. Hass concluded that the formation of multinucleated giant cells is a consequence of hydrolysis with the liberation of an acid having a melting point above the tissue environment.

Pinkerton [15] observed that cod liver oil after a prolonged stay in the lungs of rabbits became insoluble in the usual fat solvents and acquired marked affinity for carbolfuchsin. Hass [17] investigated these changes and

16. Sabin, F. R.; Doan, C. A., and Forkner, C. E.: J. Exper. Med., 1930, supp. 3, p. 1.

17. Hass, G. M.: Arch. Path. **26**:1183 and 1196, 1938.

concluded that the quantity, rate of formation and physical character of the insoluble materials depend on the structure of the compounds from which they arise. They appear at the interphase of the injected compounds and regional tissues, gradually increase in amount and form extended membranes, globules and granules. Results with (*a*) crude and acid-free cod liver and linseed oils, (*b*) the total fatty acids and unsaturated fatty acid fractions of cod liver, liver and linseed oils, (*c*) methyl esters of the unsaturated fatty acids of cod liver and linseed oils, (*d*) synthetic glycerides of the unsaturated fatty acid fraction of cod liver oil and (*e*) methyl esters of purified linoleic and linolenic fatty acids led Hass to conclude that at least two unconjugated ethylenic links in a long carbon chain of an acid or an acyl group are required before this transformation is possible. If an acid contains more than two unconjugated ethylenic links, the chemical structure is favorable for a more rapid and complete transformation. The tissue reactions caused by chaulmoogra oil, the ethyl esters of the various fatty acids of chaulmoogra oil and the ethyl ester of hydnocarpic acid, the most active principle of chaulmoogra oil, have been described.[18] All of these cyclopentenyl fatty acid esters produced abscesses or marked scar tissue reaction. Frazier and Chen [19] reported that the serial intravenous administration of doses of the ethyl esters of chalmoogra oil, comparable to those administered therapeutically to man in the treatment of leprosy, produced in the lungs of rabbits a generalized induration with widespread destruction of the parenchyma.

The cholesterol esters of the fatty acids occupy a significant position in systemic disorders of lipid metabolism, such as those in Schüller-Christian disease, xanthomatosis, focal xanthoma and atherosclerosis. Chemical analyses of these lesions demonstrate that although cholesterol and notably the cholesterol esters of the fatty acids are found in large quantities, the lipid deposits are mixtures. The lipid deposits of xanthoma, according to Harbitz [20] and others, occur in the subcutaneous tissues; the fascia; the tendon sheaths, particularly those about the knees and elbows; in the hands; in the gluteal region, and on and about the tendons at the heel. Deposits occur also in the internal organs, including the arteries.[21] The nature of the constitutional anomaly in these patients is disputed. Harbitz, citing patients whose blood had the normal quantity of cholesterol, stated that in some, apparently, deposition of cholesterol or of its esters occurs even when the content of these substances in the blood is normal. Cholesteremia, however, is regarded as important. Deposition of the lipids in definite systems indicates

18. Read, B. E.: J. Biol. Chem. **62**:515, 1924. Engelbreth-Holm, J.: Klin. Wchnschr. **13**:1605, 1934.

19. Frazier, C. N., and Chen, F. K.: Philippine J. Sc. **42**:269, 1930.

20. Harbitz, F.: Arch. Path. **4**:507, 1927.

21. Müller, C.: Arch. Int. Med. **64**:675, 1939.

peculiar cell affinities for these substances. In addition to the connective tissue cells of particular locations, the reticuloendothelial cells of the liver, spleen, lymph nodes and other places also have the deposits. Rowland,[22] in a review of these disorders, stated that all of the varied manifestations of xanthoma can be reduced to an infiltration of the reticuloendothelial system by certain lipid substances. According to this, the lesions in xanthoma are phagocyte reactions for the removal of lipids in excess or of such chemical composition that they are not readily metabolized. The lipids released into the tissues by disintegration of the phagocytes then become irritants for a tissue reaction. The hyperlipemia frequently designated as the fundamental cause of the lesions of xanthoma is probably only another manifestation of the basic lipid disturbance. The analyses of tissues in Schüller-Christian disease reported by Cowie and Magee[23] disclose changes of lipid content only in regions with the xanthoma masses. These lesions had a high content of lipids, 40 to 50 per cent of which was cholesterol. The phospholipid content was much lower than that in other tissues of the body and in normal tissues, with the exception of voluntary muscle. The phospholipid content of a xanthoma of the femur, however, was distinctly greater than that of the marrow fat and about twice as great as that of a xanthoma of the dura. Cowie and Magee tabulated the lipid analyses of human tissues and xanthoma lesions published in other reports. Wood and Reinstein[24] reported the chemical analysis of a liver in xanthomatosis. The total cholesterol was increased greatly; the total phospholipids, the sphingomyelin, the lecithin and the total fatty acids were decreased, and the cephalin was increased. The specific cellular structures produced in the ultimate tissue lesion by the individual components of such lipid mixtures cannot be decided. Cholesterol crystals alone stimulate foreign body chronic granulation tissues.[25] Solutions of cholesterol even in considerable concentration in human fat alone or with fatty acids are removed under favorable circumstances by the tissues.[26] The crystalline cholesterol in the spontaneous lesions of human tissues doubtless has been deposited from some solvent through supersaturation of the medium by removal of the solvent, by additions of cholesterol to the system or by both. The solvent of the cholesterol in the tissues probably is a lipid, liquid at the temperature of the body. Cholesterol and its fatty acid esters, mixed with other lipids, are distributed in tissue fluids in a fine emulsion.[27] Phagocytic cells in the tissues apparently remove these particles of lipid mixtures from the blood, for experimentally[28] in rabbits colloidal dispersions of cholesteryl

22. Rowland, R. S.: Arch. Int. Med. **42**:611, 1928.
23. Cowie, D. M., and Magee, M. C.: Arch. Int. Med. **53**:391, 1934.
24. Wood, H., and Reinstein, H.: Arch. Path. **30**:533, 1940.
25. Le Count, E. R.: J. M. Research **7**:166, 1902.
26. Hirsch, E. F.: Arch. Path. **25**:35, 1938.
27. Bruger, M.: J. Biol. Chem. **108**:463, 1935.
28. Hirsch, E. F., and Weinhouse, S.: Arch. Path. **30**:1079, 1940.

oleate quickly leave the blood and the lipid particles are found in the phagocytes of the liver, spleen, lungs and other tissues. In contrast, coarse droplets of cholesteryl oleate lodged in the tissues stimulate a foreign body granulation tissue reaction. The degree of dispersion of the lipid material and its chemical and physical nature apparently have importance in determining the ultimate character of the tissue reaction, the finely dispersed particles being engulfed by the phagocytes, and the larger masses of the same chemical composition stimulating a reactive tissue. Kimmelstiel and Laas [29] came to a similar conclusion in their studies of the differences in tissue reactions between pure lipids. Cholesterol, they stated, produced a fibroblastic tissue reaction; cerebrosides, a pseudoxanthoma cell reaction, and lecithin, polyblastic granulation tissues. With mixtures of the lipids, the individual tissue characteristics disappeared and a differentiation was impossible. All of the mixtures mentioned produced a pseudoxanthoma cell reaction. This loss of type differences with the lipid mixtures led Kimmelstiel and Laas to believe that the chemical character of a lipid alone is not the determining factor of the tissue lesion. The fibroblastic reaction with giant cells caused by cholesterol, they stated, depends on the crystalline character of the injected material and is merely the tissue response against an insoluble substance, a reaction not produced when cholesterol is mixed with lecithin and is highly dispersed. The type of xanthoma cell, then, depends on the colloidal dispersion of the lipid and not on its chemical character.

A recent survey and chemical study of the lipid deposits in the intima and media of the aorta with atherosclerosis by Weinhouse and Hirsch [30] emphasized that these deposits are mixtures of cholesterol, cholesterol esters, phospholipids and neutral fats. They observed that the lipid content of the media increased with age, an increase unrelated to the degree of atherosclerosis of the intima. The intima without lesions had larger amounts of lipid than the corresponding media. As the atherosclerotic lesions of the intima developed in severity, the proportions of free and combined cholesterol increased until the onset of necrosis; then the proportion of combined cholesterol decreased. These lesions also had increased proportions of ether-insoluble phospholipids and decreased proportions of ether-soluble phosphatides, galactosides and fatty acids. Weinhouse and Hirsch noted also that the proportions of the individual lipid constituents in the intima and in the simple fatty deposits of the intima corresponded closely with those reported for these lipids in the blood plasma. These relations, they concluded, imply that the lipid deposits in the intima are the result of nonselective infiltration and precipitation of lipids from the plasma of the blood.

29. Kimmelstiel, P., and Laas, E.: Beitr. z. path. Anat. u. z. allg. Path. **93**: 417, 1934.

30. Weinhouse, S., and Hirsch, E. F.: Arch. Path. **29**:31, 1940.

The effect of lipid mixtures, such as human fat, fatty acids, soap and cholesterol, on arterial tissues was investigated by Christianson.[31] The technical difficulties encountered were considerable, and the lipids injected usually lodged in the media and not in the intima. The presence of these lipid substances, however, produced vascular lesions dependent on the lipid composition. Human fat and fatty acids caused marked acute inflammatory lesions that healed rapidly. Human fat mixed with calcium soaps or with cholesterol was absorbed slowly and caused a chronic lesion, reduced finally to scar tissues. Fibrous plaques formed in the intima over the lesion in the media.

Epstein [32] proposed that the three forms of systemic lipid disorders be designated according to the lipid predominant in the deposits. Thus the Schüller-Christian disorder was termed cholesterol cell lipoidosis; Gaucher disease, a cerebroside (kerasin) cell lipoidosis, and Niemann-Pick disease, a phosphatide cell lipoidosis.

In the Niemann-Pick lipoidosis of infants the lipid deposits, according to the comprehensive summary by Baumann, Klenk and Scheidegger,[33] consist of phosphatides, cholesterol, neutral fats and fatty acids. The high phosphatide content of the various tissues is due to the marked increase of the sphingomyelin. The large so-called Pick cells in the viscera are not only reticulum cells and clasmatocytes but, in the liver and kidneys, also epithelium. The sphingomyelin fraction of the lipid deposits in the liver and spleen reported by Baumann, Klenk and Scheidegger was a mixture of palmito, stearo, lignociro and nervono sphingomyelin. The content of the monoaminophosphatides, lecithin and cephalin, equaled that of normal tissues. Chargaff's [34] analysis of a spleen with Niemann-Pick disease confirmed the opinion that the phosphatide deposits are a mixture of sphingomyelins. The sphingomyelin which he recovered in large amounts from the spleen on hydrolysis yielded sphingosine, lignoceric acid and a mixture of palmitic and stearic acids. Seventy per cent of the monoaminophosphatides was cephalin. Baumann, Klenk and Scheidegger stated that the deposition of the lipids in the various tissue cells depends on a primary intermediary cellular dysfunction. The phosphatide deposition is not the result of storage from an excess in the blood but a disturbance in the dissimilatory phase of phosphatide metabolism in the cells. Chargaff [34] and Ferraro and Jervis [35] supported this idea of a basic disorder in the metabolic disturbance. According to Baumann, Klenk and Scheidegger, the cer-

31. Christianson, O. O.: Arch. Path. **27**:1011, 1939.

32. Epstein, E.: Virchows Arch. f. path. Anat. **281**:152, 1931.

33. Baumann, T.; Klenk, E., and Scheidegger, S.: Ergebn. d. allg. Path. u. path. Anat. **30**:183, 1936.

34. Chargaff, E.: J. Biol. Chem. **130**:503, 1939.

35. Ferraro, A., and Jervis, G. A.: Arch. Path. **30**:731, 1940.

amides are the primary lipids of both the Niemann-Pick and the Gaucher disease. The cerebrosides are galactosides of ceramides; the sphingomyelin is a diaminophosphatide derived from the ceramides through esterification with choline–phosphoric acid. In Niemann-Pick disease the choline phosphate is added to the ceramide to form the main lipid, sphingomyelin; in Gaucher's disease, galactose is added to the ceramide to form kerasin. The lipid content of the blood in Niemann-Pick disease is increased, but the sphingomyelin fraction is within the range reported for normal adults.[33] The elevation of the lecithin and cholesterol content of the blood in some patients is regarded as secondary to an excretory process or an excessive release from diseased tissue cells. Ferraro and Jervis studied the effects of intravenous injections of emulsified sphingomyelin in rabbits and a monkey. The changes in the tissues resembled those of Niemann-Pick disease. They believed that the foam (Pick) cells of the spleen and bone marrow originated from the reticulum, those of the liver from the Kupffer cells, and those in the adrenal gland from the capillaries. In the lungs, histiocytes rather than epithelial cells gave rise to the characteristic cells. Ferraro and Jervis were unable to decide whether the tendency to form foam cells depends on the chemical constitution of the lipid injected or on its colloidal character. They stated that, according to Sjövall, injections of lecithin produce foam cells only temporarily, and they confirmed the statement of Baumann and Gruber that cephalin fails to produce any tissue reaction.

Analyses of liver and spleen tissues from patients with Gaucher's disease demonstrate that the lipid deposits in this disorder also are mixtures. Lieb and Mladenovič[36] identified large amounts of kerasin, a cerebroside, in the spleen involved in Gaucher's disease, an observation verified later by many others. Epstein[32] reported kerasin in the amount of 10 per cent of the dry weight in the spleen involved in Gaucher's disease. Kimmelstiel and Laas found 9.7 per cent cerebroside, in contrast with 2.4 per cent in the normal spleen. Their analysis demonstrated also more than double the amount of phosphatides of the normal spleen, although not so much as in the spleens from patients with Niemann-Pick disease. The liver and spleen involved in Gaucher's disease analyzed by Marberg[37] contained, respectively, 27.2 and 34.0 per cent lipids in relation to the total dry weights. The lipids were distributed as follows:

	Cholesterol, %		Phosphatides, %	Cerebrosides, %	Fats, Fatty
	Free	Ester	(as Lecithin)	(as Kerasin)	Acids, etc., %
Spleen.....	4.5	1.2	44.9	43.6	5.8
Liver.....	5.6	1.6	39.6	36.6	25.6

36. Lieb, H., and Mladenovič, M.: Ztschr. f. physiol. Chem. **140**:305, 1924; abstracted, Chem. Abstr. **19**:677, 1925.

37. Marberg, cited by Aballi, A. J., and Kato, K.: J. Pediat. **13**:364, 1938.

Halliday, Deuel, Tragerman, and Ward [38] reported a maximum of 6 per cent sphingomyelin in the cerebroside material recovered from the spleen of a patient with Gaucher's disease. They were interested primarily in determining the nature of the carbohydrate in the complex cerebroside. The cerebroside substance in the spleen involved in Gaucher's disease which Lieb and Mladenovič identified as kerasin contained the carbohydrate galactose. In the products of hydrolysis of the kerasin they identified lignoceric acid, sphingosin and d-galactose. Other also have reported the presence of galactose in the kerasin cerebroside. Halliday, Deuel, Tragerman and Ward discussed the methods used in the identification of kerasin and stated that less attention had been given to the nature of the carbohydrate, probably because the cerebrosides isolated from the brain were found repeatedly to contain galactose. Halliday, Deuel, Tragerman and Ward, however, found dextrose rather than galactose as the carbohydrate component of the cerebroside isolated from the spleen affected by Gaucher's disease. In other respects the cerebroside resembled kerasin.

Kimmelstiel and Laas injected a 5 per cent colloidal suspension of cerebroside into the veins of rabbits and found the lipid deposited in the reticulum cells of the spleen and the sinusoids of the liver. The spleen of rabbits killed two days after serial injections of over 7 Gm. of the lipid in three weeks had so many cells like Gaucher's cells that only traces of the normal structure remained. In 2 rabbits killed later the large storage cells in the spleen and liver were greatly reduced in number. On the basis of these results Kimmelstiel and Laas concluded that a removal of the cerebrosides stored in the reticulum cells undoubtedly occurs, though at a relatively slow rate. Small amounts of the cerebroside phrenosin have also been reported in the spleen in Gaucher's disease.[39]

SUMMARY

An analysis of the information concerning the relation of the chemical composition of lipids to characteristic lesions in the tissues discloses that among these chemical substances the fats and their derivatives, the fatty acids, occupy a significant place. The reaction of tissues about unhydrolized fat is similar to that against an inert oil like liquid petrolatum. With hydrolysis of the fats and the liberation of fatty acids, other chemical forces are released. These include: (1) the acidity developed in the surrounding tissue medium, (2) the physical state of the fatty acid, whether solid or liquid, (3) the nature of the soaps or esters formed and (4) the chemical structure of the fatty acid. Fatty acids

38. Halliday, N.; Deuel, H. J., Jr.; Tragerman, L. J., and Ward, W. E.: J. Biol. Chem. **132**:171, 1940.

39. Capper, A.; Epstein, H., and Schless, R. A.: Am. J. M. Sc. **138**:84, 1934.

in contact with alkaline aqueous mediums abstract base ion from the tissue fluids and release hydrogen ions into them. Acute necrosis of the tissues seems to result from the acidity produced. The reaction of the tissues to the fatty acid soaps depends on the basic ion entering into the reaction and the chemical structure of the fatty acids. Many of the fatty acids produce nonspecific irritative reactions, attracting primarily fibroblasts (clasmatocytes), monocytes and epithelioid cells. Relatively insoluble soaps of these fatty acids cause the formation of foreign body giant cells. Other fatty acids, such as the liquid saturated fatty acid of the tubercle bacillus, stimulate the formation of tuberculous tissues, composed of aggregates of epithelioid cells and epithelioid giant cells. Fatty acids solid at body temperature also stimulate the formation of foreign body giant cells. Certain unsaturated fatty acids by prolonged contact with tissues become insoluble in the usual fat solvents and acquire a marked affinity for carbolfuchsin.

The cholesterol esters of the fatty acids are significant in systemic disorders of lipid metabolism, such as occur in Schüller-Christian disease and xanthomatosis, and focally in xanthoma and atherosclerosis. Though cholesterol and especially the cholesterol esters are in excess in these lesions, the lipid deposits are mixtures. An opinion, at present accepted widely, considers the xanthoma lesions as phagocyte reactions which remove lipids that are present in excess in the tissues or are of such chemical composition that they are not readily metabolized. A tissue factor influences the sites of these deposits. Lipids released into the tissues by disintegration of the phagocytes then become irritants causing a reactive tissue response. Cholesterol separating in crystalline form from such lipid systems acts as an inert foreign substance. The degree of colloidal dispersion also seems to be a factor in determining the ultimate tissue reaction. Small particles of emulsified lipids are taken up by the tissue phagocytes, and large aggregates of the same chemical composition stimulate a reactive tissue.

The lipids in deposits of Niemann-Pick disease and Gaucher disease also are mixtures, apparently in colloidal dispersion, which are taken up by the reticulum and other cells of the body. The deposits in Niemann-Pick disease have a high phosphatide content, mainly sphingomyelin; those of Gaucher's disease have a high cerebroside content, chiefly kerasin. Other lipids, however, are associated with both deposits. Both diseases seem to be a primary intermediary cellular dysfunction, in which, according to Baumann, Klenk and Scheidegger, the primary chemical substance is a ceramide. In Niemann-Pick disease choline phosphate is added to the ceramide to form the main lipid, sphingomyelin; in Gaucher's disease, galactose, or dextrose according to some, is added to the ceramide to produce the kerasin.

Notes and News

Awards and Prizes.—The Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, has awarded the Katherine Berkan Judd prize of $1,000 for 1939 to E. L. Kennaway and for 1940 to J. W. Cook, both of the Royal Cancer Hospital, London, England, for their work on certain coal tar derivatives which produce cancer in animals. The results of this work are regarded as of fundamental significance to the understanding of the genesis of cancer.

The 1941 John Phillips Memorial Award of the American College of Physicians has been given to William C. Stadie in recognition of his work on anoxia, cyanosis, hemoglobin and, more especially, on fat metabolism in diabetes mellitus.

The 1940 Theobald Smith Award ($1,000 and a bronze medal) has been given to Herald R. Cox, principal bacteriologist of the United States Public Health Service, for his research in rickettsial diseases and his technic for the preparation of protective vaccines against Rocky Mountain spotted fever and typhus fever.

Society News.—The American Association for Cancer Research has been incorporated pursuant to the laws of New York state. The official organ of the association is *Cancer Research*, a monthly journal made up of articles and abstracts reporting cancer research, the first number (January 1941) of which has appeared. The next meeting of the Association will be held in Chicago at the same time as the meeting of the Federation of Societies of Experimental Biology.

E. W. Goodpasture, of Vanderbilt University, has been chosen a vice president of the American Association for the Advancement of Science and chairman of the section on medical sciences.

The executive board of the American Public Health Association announces the dates of the seventieth annual meeting as Oct. 14-17, 1941. The meeting place is Atlantic City, N. J. Headquarters for the meeting will be Convention Hall. Residence headquarters will be Hotel Traymore.

The Sixth International Congress for the Unity of Science will be held at the University of Chicago from September 2 to 6 in connection with the celebration of the fiftieth anniversary of the University. The program will consist mainly of symposiums devoted to the discussion of central and frontier problems in the present state of the unification of scientific knowledge. Those who plan to attend or who wish to receive further notices of the congress are asked to communicate with Charles Morris, University of Chicago.

Book Reviews

Histopathology of the Teeth and Their Surrounding Structures. Rudolf Kronfeld, B.S., M.D., D.D.S., Professor of Dental Histology and Pathology in the Chicago College of Dental Surgery, School of Dentistry, Loyola University, Chicago. Second edition. Cloth. Pp. 504, with 438 illustrations. Price $7. Philadelphia: Lea & Febiger, 1939.

Kronfeld was among the first to write a comprehensive text on the histopathology of the teeth and their surrounding structures. The book has been revised to keep abreast of the advances of dentistry. The chapters on the histology and physiology of the dental tissues and on histologic technic are omitted in this edition, since these subjects are now treated more fully in other textbooks.

The author states that his purpose is to illustrate actual changes in tissues in certain clinical conditions by means of human material and thus facilitate the understanding of clinical problems. He has succeeded admirably, and the book is particularly useful to the practitioner as well as to the student.

The book opens with a discussion of anomalies in the shape and number of the teeth. The subject is well presented, but the chapter, which is short, could have been enlarged to include the relation of the subject to malocclusions of teeth. Chapters 2 and 3 deal with the physiologic and pathologic aspects of the calcification and formation of teeth. The negative evidence concerning withdrawal of calcium from teeth, the influence of diet on the structure and composition of adult teeth and the relationship between caries and pregnancy are matters of medical as well as of dental interest and are well discussed. Hypoplasia of the enamel is then presented from the clinical, etiologic and microscopic points of view as well as from that of its relation to dental caries. A discussion of mottled enamel is also included.

Chapters 4 to 9 are concerned primarily with histopathologic changes of dentin and pulp. Regressive changes in dentin and pulp are considered first, and in direct relation to clinical practice (e. g., secondary dentin formation following abrasion, erosion, caries, dental operations and tooth fractures). Then follows a careful consideration of dental caries. There are three chapters on the inflammatory diseases —pulpitis and acute and chronic periodontitis. The treatment is complete and yet simple. Chapter 9 describes the tissue changes following root canal therapy and is profusely illustrated. Chapters 10 to 17 are devoted to the periodontal tissues, beginning with the cementum, its genesis, structure, function and pathologic changes, followed by a chapter on the physiologic and pathologic aspects of tooth resorption. The next two chapters deal with the epithelial attachment and gingival crevice, its histologic aspects and clinical significance, and with diseases of the periodontal tissues (alveolar atrophy, gingivitis and pyorrhea). In the next three chapters are discussed the effects of normal and of excessive functional stresses and of orthodontic procedures on the periodontal tissues. Then come chapters on a variety of subjects: embedded teeth, cysts, fractures of teeth, the healing of wounds following extraction of teeth, the histologic aspects of edentulous jaws, Vincent's infection, intrinsic and extrinsic stains and some common diseases of the oral mucosa. The last chapter really is a complete treatise on tumors of the oral cavity. In an addendum the differential diagnosis of toothache (pulpal, periodontal and gingival) is discussed, as well as the differential diagnosis of cysts of the oral cavity. This addition is helpful for the student as well as for the practitioner.

Kronfeld's book gives an authoritative and comprehensive account of dental histopathology. The book will long remain a leader in its field. The subject matter has been rearranged to conform with the suggestions in the report of the

Curriculum Survey of the American Association of Dental Schools. The style is clear, concise and interesting. The illustrations, increased to 438, mostly from Kronfeld's own material, are first class and highly instructive. The references have been selected with special care. The book might have been improved by more consideration of the normal and the pathologic aspects of the eruption of teeth (as an aid to children's dentistry) and of malocclusion. The latter is becoming more and more the concern of the general practitioner, and as yet no adequate text on the subject is available.

Age Morphology of Primary Tubercles. Henry C. Sweany, M.D., medical director of research, City of Chicago Municipal Tuberculosis Sanitarium, and research associate, University of Chicago. Cloth. Pp. 265, with 72 plates and 26 charts. Price $5. Springfield, Ill., and Baltimore: Charles C. Thomas, Publisher, 1941.

Sweany has undertaken the difficult task of determining the age of primary tubercles in the lung. By a combination of morphologic study of tubercles and careful investigation of the past history of patients examined post mortem, with a view to ascertaining the period of life at which first infection probably occurred, he has estimated the number of months or years of existence of a large number of primary tubercles. His approach is logical and the results impressive.

The validity of a conclusion as to the age of a lesion obviously depends on the accuracy of the estimate of the time of onset. Hence, logically, Sweany began with cases in which the probable error in this respect was slight. In the first chapter he analyzed a group of cases in which all the evidence available indicated that close contact with patients suffering from active tuberculosis began and ended within the first seven years of life. The total life span of the patients in this series varied from a few months to 51 years. Many patients were less than 6 years old, and hence the oldest tubercle found could not have exceeded this number of years in its age. In the majority of such cases the period of heavy exposure to tuberculosis was short, accurately known and terminated by the death of the source patient. In such cases the error in estimating the age of the oldest tubercle studied must have been small. Sweany appears to have been conservative in estimating the maximum mistake in his determinations of the age of tubercles in patients dying between 6 months and 20 years of age at ± 25 per cent.

In a series of protocols, accompanied by excellent illustrations from roentgen films, gross specimens and histologic slides, Sweany has shown the succession of changes occurring in primary tubercles from the early infiltration of cells of inflammation at the site of infection to late events, the latter characterized by deposition of calcium, ossification and subsequent resorption of bone. After learning with a reasonable degree of accuracy the length of time consumed by the different phases of development, by the maturation and by the regression, and the significance of the several anatomic elements making up the complex structure of an old tubercle, he constructed a chart in which these elements were weighted for calculation of the probable age in cases in which the early history of exposure was not well known.

Careful morphologic studies of primary tubercles of obviously varying age have been made by previous investigators, but no previous investigation has been supported by such detail on past history of infection. In this respect Sweany's investigation is of exceptional value. The basic considerations in instances in which the past history was well known appear to be sound and afford confidence in Sweany's interpretation of lesions discovered in cases in which the early history was obscure.

Sweany's conclusions are subject to question chiefly because they were drawn from cases in which the patients died from tuberculosis. The cases were thus highly complex, with much recent tuberculosis superimposed on the old tuberculosis under consideration. Had it been possible to make a corresponding study of

primary tubercles in the lungs of patients free from tuberculosis of later life, his conclusions would be free from doubt. However, in actual practice the difficulty in distinguishing primary and subsequent tubercles appears not to have been great.

The author is to be congratulated on his success. In this the publisher has played an important part. The format is attractive, the style of print makes reading easy and the illustrations are excellent.

Clinique et physiopathologie des maladies coeliaques. Robert Dubois, agrégé de l'enseignement supérieur médecin adjoint de la Clinique infantile de l'Université de Bruxelles. Préface de E. J. Bigdoow, professeur a l'Université de Bruxelles. Paper. Price, 80 francs. Pp. 350. Paris: Masson & Cie, 1939.

Since Gee's original description, in 1888, celiac disease has attracted the attention of clinicians and of physiologists, but the nature of the underlying conditions was little understood until relatively recent years. In this monograph the entire literature is reviewed and an attempt is made to correlate recent experimental studies, particularly those of the physiologist Verzár, with clinical observations. Celiac disease of childhood and nontropical sprue of the adult are considered identical by many authorities, and, according to Verzár, both are due to a disorder of the adrenal glands. This hypothesis, as well as the observations on metabolic disturbances due to intoxication of animals with monoiodoacetic acid, are critically analyzed, and an attempt is made to explain with their help some of the obscure aspects of the disease. The causes, the morphologic aspects, the findings in the stools, the roentgenologic changes, the metabolism of fats, carbohydrates, water, phosphorus and calcium, the acid-base equilibrium, the hematologic changes and the undoubtedly grave vitamin deficiencies, particularly of vitamin B_2, are presented in detail, and the disease is explained convincingly as resulting from a fundamental disturbance of the selective absorptive properties of the small intestine. The meagerness of present knowledge of the pathologic anatomy of the disease is stressed. All this is built around a study of 6 patients —4 children with celiac disease and 2 adults with nontropical sprue. The clinical observations on these patients, the very painstaking chemical investigations of the blood, stools and urine and the excellently reproduced and analyzed roentgenologic films deserve commendation, not only for their thoroughness but also for the good use to which they were put. One child died, and the observations at autopsy are recorded.

This monograph shows that a thorough study of a small material is apt to be more fruitful in results than a superficial consideration of a large amount of data.

Whoever wishes to become acquainted with all that is known at present on the subject of celiac disease can find no better guide than Dubois' book. A well selected bibliography is appended.

Books Received

COLLECTED STUDIES OF SKIN DISEASES. Dermatological Departments of the Barnard Free Skin and Cancer Hospital and the Washington University School of Medicine, St. Louis. Edited by M. F. Engman Sr., M.D. Pp. 276. Washington University Studies—New Series, Science and Technology—no. 10. St. Louis: Washington University, 1940.

HEMORRHAGIC DISEASES. PHOTO-ELECTRIC STUDY OF BLOOD COAGULABILITY. Kaare K. Nygaard, M.D., former fellow in surgery, the Mayo Foundation, Rochester, Minn.; former assistant in surgery, the University Clinic, Oslo, Norway. Pp. 320, with 59 figures. St. Louis: C. V. Mosby Company, 1941.

THE PERIODICITY AND CAUSE OF CANCER, LEUKAEMIA AND ALLIED TUMOURS WITH CHAPTERS ON THEIR TREATMENT. J. H. Douglas Webster, M.D., F.F.C.P.E., F.F.R., honorary director, Meyerstein Institute of Radiotherapy, Middlesex Hospital, London, England. Pp. 178, with plates and charts. Price $3.50. Baltimore: Williams & Wilkins Company, 1940.